

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
29 May 2008 (29.05.2008)

PCT

(10) International Publication Number
WO 2008/064315 A1

(51) International Patent Classification:

C07D 271/06 (2006.01) *A61K 31/137* (2006.01)
C07D 233/16 (2006.01) *A61K 31/381* (2006.01)
C07D 413/04 (2006.01) *A61K 31/4245* (2006.01)
C07C 215/38 (2006.01) *A61P 19/00* (2006.01)

(21) International Application Number:

PCT/US2007/085392

(22) International Filing Date:

21 November 2007 (21.11.2007)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/860,696 21 November 2006 (21.11.2006) US
60/956,376 16 August 2007 (16.08.2007) US

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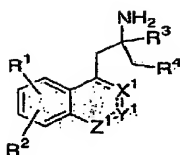
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(54) Title: TETRALIN ANALOGS HAVING SPHINGOSINE 1-PHOSPHATE AGONIST ACTIVITY



(57) Abstract: Tetralin analogs that have agonist activity at one or more of the SIP receptors are provided. The compounds are sphingosine analogs, which, after phosphorylation, can behave as agonists at SIP receptors.



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TETRALIN ANALOGS HAVING SPHINGOSINE 1-PHOSPHATEAGONIST ACTIVITYCross-Reference to Related Applications

[0001] This application claims priority to Provisional Application Nos. 60/956,376, filed August 16, 2007 and Application Serial No. 60/860,696, filed November 21, 2006, the disclosures of all of which are incorporated by reference in their entirety.

US Government Rights

[0002] This invention was made with United States Government support under Grant No. RO1 GM 067958 awarded by the National Institutes of Health. The United States Government may have certain rights in the invention.

Background of the Invention

[0003] Sphingosine 1-phosphate (S1P) is a lysophospholipid mediator that evokes a variety of cellular responses by stimulation of five members of the endothelial cell differentiation gene (EDG) receptor family. The EDG receptors are G-protein coupled receptors (GPCRs) and on stimulation propagate second messenger signals via activation of heterotrimeric G-protein alpha (G_{α}) subunits and beta-gamma ($G_{\beta\gamma}$) dimers. Ultimately, this S1P-driven signaling results in cell survival, increased cell migration and, often, mitogenesis. The recent development of agonists targeting S1P receptors has provided insight regarding the role of this signaling system in physiologic homeostasis. For example, the immunomodulator, FTY720 (2-amino-2-[2-(4-octylphenyl) ethyl] propane 1,3-diol), that following phosphorylation, is an agonist at 4 of 5 S1P receptors, revealed that enhancing S1P tone influences lymphocyte trafficking. Further, S1P type 1 receptor (S1P₁) antagonists cause leakage of the lung capillary endothelium, which suggests that S1P may be involved in maintaining the integrity of the endothelial barrier in some tissue beds.

[0004] Sphingosine 1-phosphate (S1P) is a lysophospholipid mediator that evokes a variety of cellular responses by stimulation of five members of the endothelial cell differentiation gene (EDG) receptor family.

[0005] Sphingosine-1-phosphate (S1P) has been demonstrated to induce many cellular processes, including those that result in platelet aggregation, cell proliferation, cell morphology, tumor-cell invasion, endothelial cell chemotaxis and angiogenesis. For these reasons, S1P receptors are good targets for therapeutic applications such as wound healing and tumor growth inhibition.

[0006] Sphingosine-1-phosphate signals cells in part via a set of G protein-coupled receptors named S1P₁, S1P₂, S1P₃, S1P₄, and S1P₅ (formerly EDG1, EDG5, EDG3, EDG6 and EDG8). The EDG receptors are G-protein coupled receptors (GPCRs) and on stimulation propagate second messenger signals via activation of heterotrimeric G-protein alpha (G α) subunits and beta-gamma (G $\beta\gamma$) dimers. These receptors share 50-55% amino acid sequence identity and cluster with three other receptors (LPA₁, LPA₂, and LPA₃ (formerly EDG2, EDG4 and EDG7) for the structurally related lysophosphatidic acid (LPA).

[0007] A conformational shift is induced in the G-Protein Coupled Receptor (GPCR) when the ligand binds to that receptor, causing GDP to be replaced by GTP on the α -subunit of the associated G-proteins and subsequent release of the G-proteins into the cytoplasm. The α -subunit then dissociates from the $\beta\gamma$ -subunit and each subunit can then associate with effector proteins, which activate second messengers leading to a cellular response. Eventually the GTP on the G-proteins is hydrolyzed to GDP and the subunits of the G-proteins reassociate with each other and then with the receptor. Amplification plays a major role in the general GPCR pathway. The binding of one ligand to one receptor leads to the activation of many G-proteins, each capable of associating with many effector proteins leading to an amplified cellular response.

[0008] S1P receptors make good drug targets because individual receptors are both tissue and response specific. Tissue specificity of the S1P receptors is desirable because development of an agonist or antagonist selective for one receptor localizes the cellular response to tissues containing that receptor, limiting unwanted side effects. Response specificity of the S1P receptors is also of importance because it allows for the development of agonists or antagonists that initiate or suppress certain cellular responses without affecting other responses. For example, the response specificity of

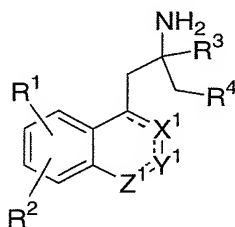
the S1P receptors could allow for an S1P mimetic that initiates platelet aggregation without affecting cell morphology.

[0009] Sphingosine-1-phosphate is formed as a metabolite of sphingosine in its reaction with sphingosine kinase and is stored in abundance in the aggregates of platelets where high levels of sphingosine kinase exist and sphingosine lyase is lacking. S1P is released during platelet aggregation, accumulates in serum, and is also found in malignant ascites. Reversible biodegradation of S1P most likely proceeds via hydrolysis by ectophosphohydrolases, specifically the sphingosine 1- phosphate phosphohydrolases. Irreversible degradation of S1P is catalyzed by S1P lyase yielding ethanolamine phosphate and hexadecena

[0010] Currently, there is a need for novel, potent, and selective agents that are agonists of the S1P receptor having enhanced potency, selectivity, and oral bioavailability. In addition, there is a need in the art for identification of, as well as the synthesis and use of such compounds. The present invention satisfies these needs.

Summary

[0011] The present invention provides in one aspect compounds that have agonist activity at one or more of the S1P receptors. The compounds are sphingosine analogs that, after phosphorylation, can behave as agonists at S1P receptors. Accordingly, there is provided compounds of Formula I:

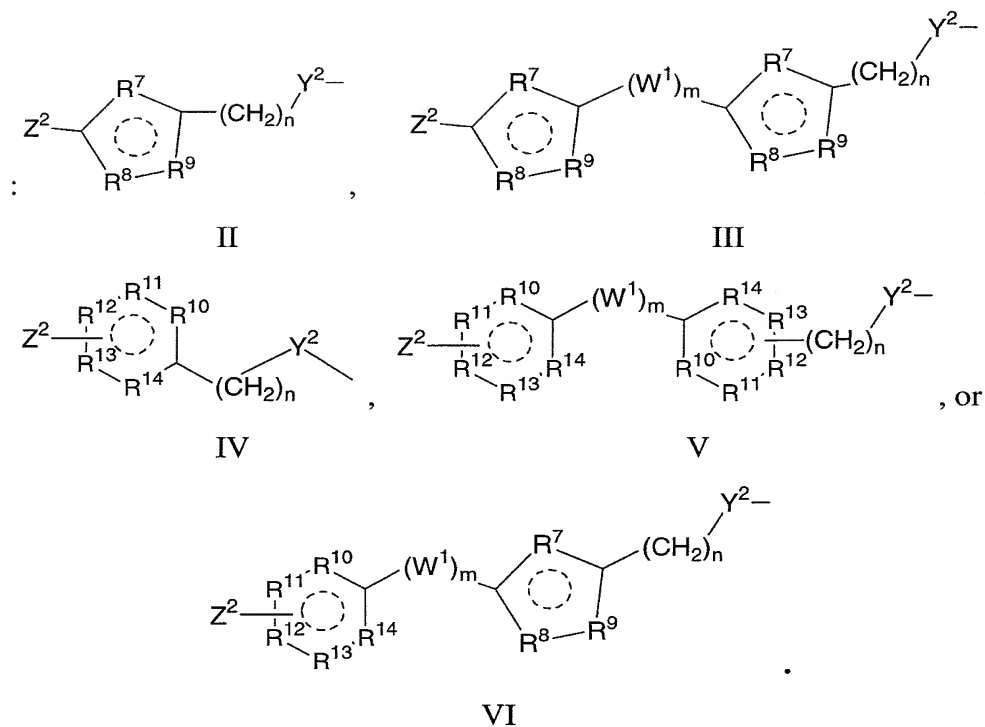


I

wherein X^1 , Y^1 and Z^1 are independently O, CR^a , CR^aR^b , N, NR^c , or S.

R^1 and R^2 are independently hydrogen, halo, halo(C_1 - C_{10})alkyl, cyano, $-NR^aR^b$, (C_1 - C_{20})alkyl, (C_2 - C_{20})alkenyl, (C_2 - C_{20})alkynyl, (C_1 - C_{20})alkoxy, (C_2 - C_{26})alkoxyalkyl, (C_3 - C_{12})cycloalkyl, (C_6 - C_{10})aryl, (C_7 - C_{30})arylalkyl, (C_2 - C_{10})heterocyclic, (C_4 - C_{10})heteroaryl, or (C_4 - C_{10})heteroaryl(C_1 - C_{20})alkyl; or

R^2 can be a group having Formula II, III, IV, V, or VI:



wherein each R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, and R¹⁴ is independently O, S, C, CR¹⁵, CR¹⁶R¹⁷, C=O, N or NR¹⁸; and

each R¹⁵, R¹⁶ and R¹⁷ is independently hydrogen, halo, (C₁-C₁₀)alkyl, (C₆-C₁₀)aryl, (C₁-C₁₀)alkyl substituted with halo, hydroxy, (C₁-C₁₀)alkoxy, or cyano; and where R¹⁸ can be hydrogen or (C₁-C₁₀)alkyl;

Z^2 is hydrogen, halo, halo(C_1 - C_{10})alkyl, cyano, $-NR^aR^b$, (C_1 - C_{20})alkyl, (C_2 - C_{20})alkenyl, (C_2 - C_{20})alkynyl, (C_1 - C_{20})alkoxy, (C_2 - C_{26})alkoxyalkyl, (C_3 - C_{12})cycloalkyl, (C_6 - C_{10})aryl, (C_7 - C_{30})arylalkyl, (C_2 - C_{10})heterocyclic, (C_4 - C_{10})heteroaryl, or (C_4 - C_{10})heteroaryl(C_1 - C_{20})alkyl. The alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclic, or heteroaryl groups of Z^2 are optionally perfluorinated or optionally substituted with 1, 2, 3, or 4 groups where the substituent groups are independently hydroxy, halo, cyano, (C_1 - C_{10})alkoxy, C_6 -aryl, (C_7 - C_{24})arylalkyl, oxo ($=O$), or imino ($=NR^d$), wherein one or more of the carbon atoms in the Z^2 alkyl groups can be independently replaced with non-peroxide oxygen, sulfur or NR^c ;

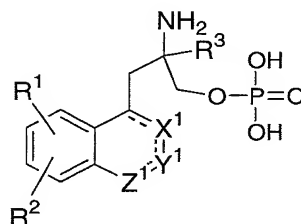
○ indicates one or more optional double bonds;

Y² is a bond (absent), O, S, C=O, or NR^c, CH₂; W¹ is a bond (absent); -CH₂- and m is 1, 2, or 3, or (C=O)(CH₂)₁₋₅ and m is 1; wherein W¹ is optionally interrupted with non-peroxide O, S, C=O, or NR^c. Each --- represents an optional double bond; and n is 0, 1, 2, or 3.

[0012] R^3 is hydrogen, (C_1-C_{10}) alkyl, hydroxy (C_1-C_{10}) alkyl or (C_1-C_{10}) alkoxy; and R^4 is hydroxy $(-OH)$, phosphate $(-OPO_3H_2)$, phosphonate $(-CH_2PO_3H_2)$, or *alpha*-substituted phosphonate. Each R^a , R^b , R^c , and R^d is independently hydrogen, or (C_1-C_{10}) alkyl.

[0013] The alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclic, or heteroaryl groups of R^1 and R^2 independently are optionally perfluorinated or optionally substituted with 1, 2, 3, or 4 groups where the substituent groups are independently hydroxy, halo, cyano, (C_1-C_{10}) alkoxy, C_6 -aryl, (C_7-C_{24}) arylalkyl, oxo $(=O)$, or imino $(=NR^d)$, wherein one or more of the carbon atoms in the R^1 or R^2 alkyl groups can be independently replaced with non-peroxide oxygen, sulfur or NR^c . The alkyl groups of R^3 are optionally substituted with 1, or 2 hydroxy groups; and R^d is hydrogen, or (C_1-C_{10}) alkyl. The invention includes pharmaceutically acceptable salts or esters of the compounds of Formula I.

[0014] In another aspect, the invention provides phosphate monoesters having Formula VIII.



VIII

where R^1 , R^2 , R^3 , X^1 , Y^1 , and Z^1 are as defined above. In another aspect, the invention provides enantiomers and stereoisomers of the compounds having Formulas I, or VIII.

[0015] In another aspect, the invention provides pro-drugs of the compounds of Formula I. The invention also provides compounds of Formula I or pharmaceutically acceptable salts or esters thereof for use in medical therapy.

[0016] In another aspect, the present invention provides a method for inhibiting angiogenesis in a tumor, comprising contacting the cancerous cells with an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

[0017] In another aspect, the invention provides a method for modulating the immune system by altering lymphocyte trafficking for treatment of autoimmune diseases or prolongation of allograft transplant survival, said method comprising

administering an effective amount of at least one compound of the invention to a subject in need thereof.

[0018] In another aspect, the invention provides a method for treating neuropathic pain, wherein a pharmaceutical composition comprising an effective amount of at least one compound of the invention and a pharmaceutically-acceptable carrier is administered to a subject in need thereof.

[0019] In another aspect, the invention provides a method for repairing vascular injury following catheterization, comprising contacting the lumen of the affected vessel with an effective amount of the compound of Formula I. In another aspect, the invention includes coating indwelling stents with a compound of Formula I.

[0020] In another aspect, the invention provides a compound of Formula I, or a pharmaceutically acceptable salt thereof for use in medical treatment (for example, treatment of neoplastic disease, treatment of neuropathic pain, treatment of autoimmune disease, prolongation of allograft survival).

[0021] In another aspect, the invention provides a method for the use of a compound of Formula I or a pharmaceutically acceptable salt thereof to prepare a medicament for inhibiting tumor growth, metastasis or tumor angiogenesis in a mammalian species (for example, a human).

[0022] In another aspect, the invention provides for the use of a compound of Formula I or a pharmaceutically acceptable salt thereof to prepare a medicament for treating an autoimmune disease or prolonging allograft survival in a mammalian species (for example, a human).

[0023] In another aspect, the invention provides for the use of a compound of Formula I or a pharmaceutically acceptable salt thereof to prepare a medicament for treating neuropathic pain in a mammalian species (for example, a human).

[0024] In another aspect, the invention provides a method for assessing a compound of Formula I (*e.g.*, S1P receptor pro-drugs) as a substrate for sphingosine kinase types 1 or 2, *in vitro* and *in vivo*. The invention includes also a method of assessing a compound of Formula (II) for binding to designated receptor sites comprising *in vivo* or *in vitro*, with an amount of a compound of Formula (II) effective to bind said receptors. Tissue comprising ligand bound designated S1P receptor sites can be used to measure the selectivity of test compounds for specific receptor subtypes,

or can be used as a tool to identify potential therapeutic agents for the treatment of diseases, by contacting said agents with said ligand-receptor complexes, and measuring the extent of displacement of the ligand and/or binding of the agent.

[0025] In another aspect, the invention provides novel intermediates and processes disclosed herein that are useful for preparing compounds of Formula I, including the generic and specific intermediates as well as the synthetic processes described herein.

[0026] In another aspect, the present invention provides synthetic schemes and methods of use of compounds having Formula I and analogs or derivatives thereof. The invention further provides synthetic and modification schemes for preparing analogs and derivatives of the compounds of the invention, as well as compositions and methods for the use of such analogs and derivatives.

Brief Description of the Drawings

[0027] **Fig. 1** illustrate three S1P agonists FTY720, AAL151 and compound XXIX.

[0028] **Figs. 2A-2C** illustrate additional compounds of Formula I.

[0029] **Figs. 3 – 5** illustrate syntheses of compounds of Formula I.

Detailed Description

[0030] The following abbreviations are used herein: S1P, sphingosine-1-phosphate; S1P₁₋₅- S1P receptor types; GPCR, G-protein coupled receptor; SAR, structure-activity relationship; EDG, endothelial cell differentiation gene; EAE, experimental autoimmune encephalomyelitis; NOD non-obese diabetic; TNF α , tumor necrosis factor *alpha*; HDL, high density lipoprotein; and RT-PCR, reverse transcriptase polymerase chain reaction.

[0031] In describing and claiming the invention, the following terminology will be used in accordance with the definitions set forth below. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any materials and methods similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred materials and methods are described herein. As used herein, each of the following terms has meaning associated with it in this section. Specific and preferred values listed below for

radicals, substituents, and ranges are for illustrations only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

[0032] The terms “a,” “an,” “the,” “at least one,” and “one or more” are used interchangeably. Thus, for example, a composition that comprises “an” element means one element or more than one element.

[0033] The term “receptor agonists” are compounds that mimic the action of S1P at one or more of its receptors but may have differing potency and/or efficacy.

[0034] The term “receptor antagonists” are compounds that 1) lack intrinsic agonist activity and 2) block agonist (*e.g.*, S1P) activation of the S1P receptor(s), often in a manner that is both fully surmountable and reversible (‘competitive antagonist’).

[0035] The term “affected cell” refers to a cell of a subject afflicted with a disease or disorder, which affected cell has an altered phenotype relative to a subject not afflicted with a disease or disorder.

[0036] Cells or tissue are “affected” by a disease or disorder if the cells or tissue have an altered phenotype relative to the same cells or tissue in a subject not afflicted with a disease or disorder.

[0037] A disease or disorder is “alleviated” if the severity of a symptom of the disease or disorder, the frequency with which such a symptom is experienced by a patient, or both, is reduced.

[0038] An “analog” of a chemical compound is a compound that, by way of example, resembles another in structure but is not necessarily an isomer (*e.g.*, 5-fluorouracil is an analog of thymine).

[0039] The terms “cell,” “cell line,” and “cell culture” may be used interchangeably.

[0040] A “control” cell, tissue, sample, or subject is a cell, tissue, sample, or subject of the same type as a test cell, tissue, sample, or subject. The control may, for example, be examined at precisely or nearly the same time the test cell, tissue, sample, or subject is examined. The control may also, for example, be examined at a time distant from the time at which the test cell, tissue, sample, or subject is examined, and the results of the examination of the control may be recorded so that the recorded results may be compared with results obtained by examination of a test cell, tissue, sample, or subject. The control may also be obtained from another source or similar

source other than the test group or a test subject, where the test sample is obtained from a subject suspected of having a disease or disorder for which the test is being performed.

[0041] A “test” cell, tissue, sample, or subject is one being examined or treated.

[0042] A “pathoindicative” cell, tissue, or sample is one which, when present, is an indication that the animal in which the cell, tissue, or sample is located (or from which the tissue was obtained) is afflicted with a disease or disorder. By way of example, the presence of one or more breast cells in a lung tissue of an animal is an indication that the animal is afflicted with metastatic breast cancer.

[0043] A tissue “normally comprises” a cell if one or more of the cell are present in the tissue in an animal not afflicted with a disease or disorder.

[0044] The use of the word “detect” and its grammatical variants is meant to refer to measurement of the species without quantification, whereas use of the word “determine” or “measure” with their grammatical variants are meant to refer to measurement of the species with quantification. The terms “detect” and “identify” are used interchangeably herein.

[0045] A “detectable marker” or a “reporter molecule” is an atom or a molecule that permits the specific detection of a compound comprising the marker in the presence of similar compounds without a marker. Detectable markers or reporter molecules include, *e.g.*, radioactive isotopes, antigenic determinants, enzymes, nucleic acids available for hybridization, chromophores, fluorophores, chemiluminescent molecules, electrochemically detectable molecules, and molecules that provide for altered fluorescence-polarization or altered light-scattering.

[0046] A “disease” is a state of health of an animal wherein the animal cannot maintain homeostasis, and wherein if the disease is not ameliorated then the animal's health continues to deteriorate.

[0047] A “disorder” in an animal is a state of health in which the animal is able to maintain homeostasis, but in which the animal's state of health is less favorable than it would be in the absence of the disorder. Left untreated, a disorder does not necessarily cause a further decrease in the animal's state of health.

[0048] An “effective amount” means an amount sufficient to produce a selected effect. For example, an effective amount of an S1P receptor antagonist is an amount that decreases the cell signaling activity of the S1P receptor.

[0049] A “functional” molecule is a molecule in a form in which it exhibits a property by which it is characterized. By way of example, a functional enzyme is one which exhibits the characteristic catalytic activity by which the enzyme is characterized.

[0050] The term “inhibit” refers to the ability of a compound of the invention to reduce or impede a described function. Preferably, inhibition is by at least 10%, more preferably by at least 25%, even more preferably by at least 50%, and most preferably, the function is inhibited by at least 75%.

[0051] “Instructional material” includes a publication, a recording, a diagram, or any other medium of expression which can be used to communicate the usefulness of the peptide of the invention in the kit for effecting alleviation of the various diseases or disorders recited herein. Optionally, or alternately, the instructional material may describe one or more methods of alleviating the diseases or disorders in a cell or a tissue of a mammal. The instructional material of the kit of the invention may, for example, be affixed to a container which contains the identified compound invention or be shipped together with a container which contains the identified compound. Alternatively, the instructional material may be shipped separately from the container with the intention that the instructional material and the compound be used cooperatively by the recipient.

[0052] The term “parenteral” means not through the alimentary canal but by some other route such as subcutaneous, intramuscular, intraspinal, or intravenous.

[0053] The term “pharmaceutically acceptable carrier” includes any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water and emulsions such as an oil/water or water/oil emulsion, and various types of wetting agents. The term also encompasses any of the agents approved by a regulatory agency of the U.S. Federal government or listed in the U.S. Pharmacopeia for use in animals, including humans.

[0054] The term “purified” and similar terms relate to the isolation of a molecule or compound in a form that is substantially free (at least 75% free, preferably 90% free,

and most preferably at least 95% free) from other components normally associated with the molecule or compound in a native environment. The term “purified” does not necessarily indicate that complete purity of the particular molecules achieved during the process. A “very pure” compound refers to a compound that is greater than 90% pure. A “highly purified” compound refers to a compound that is greater than 95% pure.

[0055] A “sample” refers preferably to a biological sample from a subject, including, but not limited to, normal tissue samples, diseased tissue samples, biopsies, blood, saliva, feces, semen, tears, and urine. A sample can also be any other source of material obtained from a subject, which contains cells, tissues, or fluid of interest. A sample can also be obtained from cell or tissue culture.

[0056] The term “standard,” refers to something used for comparison. For example, a standard can be a known standard agent or compound which is administered or added to a control sample and used for comparing results when measuring said compound in a test sample. Standard can also refer to an “internal standard,” such as an agent or compound which is added at known amounts to a sample and is useful in determining such things as purification or recovery rates when a sample is processed or subjected to purification or extraction procedures before a marker of interest is measured.

[0057] A “subject” of analysis, diagnosis, or treatment is an animal. Such animals include mammals, preferably a human.

[0058] A “therapeutic” treatment is a treatment administered to a subject who exhibits signs of pathology for the purpose of diminishing or eliminating those signs.

[0059] A “therapeutically effective amount” of a compound is that amount of compound which is sufficient to provide a beneficial effect to the subject to which the compound is administered.

[0060] The term “treating” includes prophylaxis of the specific disorder or condition, or alleviation of the symptoms associated with a specific disorder or condition and/or preventing or eliminating said symptoms.

[0061] The disclosed compounds are generally named according to the IUPAC or CAS nomenclature system. Abbreviations which are well known to one of ordinary skill in the art may be used (*e.g.*, “Ph” for phenyl, “Me” for methyl, “Et” for ethyl, “h”

for hour or hours, "rt" for room temperature, "THF" for tetrahydrofuran, and "rac" for racemic mixture).

[0062] Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents. The compounds of the invention include compounds of Formula I having any combination of the values, specific values, more specific values, and preferred values described herein.

[0063] Specifically, the term "halogen" or "halo" includes bromo, chloro, fluoro, and iodo. The term "haloalkyl", refers to an alkyl radical bearing at least one halogen substituent, non-limiting examples include, but are not limited to, chloromethyl, fluoroethyl or trifluoromethyl and the like. The term "C₁-C₂₀ alkyl" refers to a branched or linear alkyl group having from one to twenty carbons. Non-limiting examples include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl and the like. The term "C₂-C₂₀ alkenyl", refers to an olefinically unsaturated branched or linear group having from two to twenty carbon atoms and at least one double bond. Typically, C₂-C₂₀ alkenyl groups include, but are not limited to, 1-propenyl, 2-propenyl, 1,3-butadienyl, 1-butenyl, hexenyl, pentenyl, hexenyl, heptenyl, octenyl and the like. The term (C₂-C₂₀)alkynyl can be ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentylnyl, 2-pentylnyl, 3-pentylnyl, 4-pentylnyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, or 5-hexynyl, and the like. The term "(C₁-C₂₀)alkoxy or alkoxy" refers to an alkyl group attached through an oxygen atom. Examples of (C₁-C₂₀)alkoxy can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, 3-pentoxy, hexyloxy, heptoxy, or octoxy and the like.

[0064] The term "C₃-C₁₂ cycloalkyl", can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

[0065] The term "optionally substituted" refers to from zero, one, two, three or four substituents, wherein the substituents are each independently selected. Each of the independently selected substituents may be the same or different than other substituents.

[0066] The term "(C₆-C₁₀)aryl" refers to a mono or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, benzyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl, and the like. The term "aryl" refers to a

mono or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, benzyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl, and the like.

[0067] The term “aryl(C₁-C₂₀)alkyl” or “aralkyl” refers to an alkyl group substituted with a mono or bicyclic carbocyclic ring system having one or two aromatic rings including, a group such as phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl, and the like. Non-limiting examples of arylalkyl include benzyl, phenylethyl, and the like.

[0068] The term “optionally substituted aryl” includes aryl compounds having from zero to four substituents, and a substituted aryl includes aryl compounds having one to three substituents, wherein the substituents include groups such as, for example, alkyl, halo, or amino substituents.

[0069] The “(C₂-C₁₀)heterocyclic group” refers to an optionally substituted mono- or bicyclic carbocyclic ring system containing one, two, or three heteroatoms (optionally in each ring) wherein the heteroatoms are oxygen, sulfur, and nitrogen.

[0070] The term “bicyclic” represents either an unsaturated or saturated stable 7- to 12-membered bridged or fused bicyclic carbon ring. The bicyclic ring may be attached at any carbon atom which affords a stable structure. The term includes, but is not limited to, naphthyl, dicyclohexyl, dicyclohexenyl, and the like.

[0071] The term “phosphate analog” and “phosphonate analog” comprise analogs of phosphate and phosphonate wherein the phosphorous atom is in the +5 oxidation state and one or more of the oxygen atoms is replaced with a non-oxygen moiety, including for example, the phosphate analogs phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phosphoranilidate, phosphoramidate, boronophosphates, and the like, including associated counterions, *e.g.*, H, NH₄, Na, K, and the like if such counterions are present.

[0072] The term “*alpha*-substituted phosphonate” includes phosphonate (-CH₂PO₃H₂) groups that are substituted on the *alpha*-carbon such as -CHFPO₃H₂, -CF₂PO₃H₂, -CHOHPO₃H₂, -C=OPO₃H₂) and the like.

[0073] A “derivative” of a compound refers to a chemical compound that may be produced from another compound of similar structure in one or more steps, as in replacement of hydrogen by an alkyl, acyl, or amino group.

[0074] The term “pharmaceutically acceptable carrier” includes any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, hydroxypropyl beta-cyclodextrins (HO-propyl beta cyclodextrins), water, emulsions such as an oil/water or water/oil emulsion, and various types of wetting agents. The term also encompasses any of the agents approved by a regulatory agency of the US Federal government or listed in the US Pharmacopeia for use in animals, including humans.

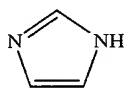
[0075] The term “pharmaceutically-acceptable salt” refers to salts which retain the biological effectiveness and properties of the compounds of the present invention and which are not biologically or otherwise undesirable. In many cases, the compounds of the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

[0076] An “effective amount” means an amount sufficient to produce a selected effect. For example, an effective amount of an S1P receptor agonist is an amount that decreases the cell signaling activity of the S1P receptor.

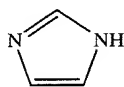
[0077] The disclosed compounds can contain one or more asymmetric centers in the molecule. In accordance with the present disclosure any structure that does not designate the stereochemistry is to be understood as embracing all the various optical isomers, as well as racemic mixtures thereof.

[0078] The disclosed compounds can contain one or more asymmetric centers in the molecule. In accordance with the present disclosure any structure that does not designate the stereochemistry is to be understood as embracing all the various optical isomers, as well as racemic mixtures thereof.

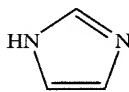
[0079] The compounds of the present invention may exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers. For example, the following structure:



is understood to represent a mixture of the structures:



as well as



[0080] The terms 16:0, 18:0, 18:1, 20:4 or 22:6 hydrocarbon refers to a branched or straight alkyl or alkenyl group, wherein the first integer represents the total number of

carbons in the group and the second integer represent the number of double bonds in the group.

[0081] An "S1P modulating agent" refers a compound or composition that is capable of inducing a detectable change in S1P receptor activity *in vivo* or *in vitro* (e.g., at least 10% increase or decrease in S1P activity as measured by a given assay such as the bioassay described in the examples and known in the art. "S1P receptor," as used herein, refers to all of the S1P receptor subtypes (for example, the S1P receptors S1P₁, S1P₂, S1P₃, S1P₄, and S1P₅), unless the specific subtype is indicated.

[0082] The disclosed compounds can contain one or more asymmetric centers in the molecule. In accordance with the present disclosure any structure that does not designate the stereochemistry is to be understood as embracing all the various optical isomers, as well as racemic mixtures thereof.

[0083] It will be appreciated by those skilled in the art that compounds of the invention having chiral centers may exist in and be isolated in optically active and racemic forms. It is to be understood that the present invention encompasses any racemic, optically active or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, such as the *S,R*; *S,S*; *R,R*; or *R,S* diastereomers. It is well known in the art how to prepare such optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine S1P agonist activity using the standard tests described herein, or using other similar tests which are well known in the art. In addition, some compounds may exhibit polymorphism.

[0084] Potential uses of an S1P receptor agonist pro-drugs (S1P₁ receptor type selective agonists preferred) include, but are not limited to, altering lymphocyte trafficking as a method of treatment for autoimmune pathologies such as uveitis, type I diabetes, rheumatoid arthritis, inflammatory bowel diseases, and, most particularly, multiple sclerosis. "Treatment" of multiple sclerosis includes the various forms of the disease including relapsing-remitting, chronic progressive, etc., and the S1P receptor agonists can be used alone or in conjunction with other agents to relieve signs and symptoms of the disease as well as prophylactically.

[0085] In addition, the disclosed compounds of the invention can be used for altering lymphocyte trafficking is a method for prolonging allograft survival, for example solid organ transplants, treatment of graft vs. host disease, bone marrow transplantation, and the like.

[0086] In addition, the disclosed compounds of the invention can be used to inhibit autotaxin. Autotaxin, a plasma phosphodiesterase, has been demonstrated to undergo end product inhibition. Autotaxin hydrolyzes several substrates to yield lysophosphatidic acid and sphingosine 1-phosphate, and has been implicated in cancer progression and angiogenesis. Therefore, S1P receptor agonist pro-drugs of the invention can be used to inhibit autotaxin. This activity may be combined with agonism at S1P receptors or may be independent of such activity.

[0087] In addition, disclosed compounds of the invention can be useful for inhibition of S1P lyase. S1P lyase is an intracellular enzyme that irreversibly degrades S1P. Inhibition of S1P lyase disrupts lymphocyte trafficking with concomitant lymphopenia. Accordingly, S1P lyase inhibitors can be useful in modulating immune system function. Therefore, the compounds of the invention can be used to inhibit S1P lyase. This inhibition could be in concert with S1P receptor activity, or be independent of activity at any S1P receptor.

[0088] In addition, disclosed compounds of the invention can be useful as antagonists of the cannabinoid CB₁ receptor. CB₁ antagonism is associated with a decrease in body weight and an improvement in blood lipid profiles. The CB₁ antagonism could be in concert with S1P receptor activity, or be independent of activity at any S1P receptor.

[0089] In addition, disclosed compounds of the invention can be useful for inhibition of group IVA cytosolic PLA₂ (cPLA₂). cPLA₂ catalyzes the release of eicosanoic acids (*e.g.* arachidonic acid). The eicosanoic acids are transformed to pro-inflammatory eicosanoids such as prostaglandins and leukotrienes. Thus compounds of the invention can be useful as anti-inflammatory agents. This inhibition could be in concert with S1P receptor activity, or be independent of activity at any S1P receptor.

[0090] In addition, disclosed compounds of the invention can be useful for inhibition of the multiple substrate lipid kinase (MuLK). MuLK is highly expressed in many human tumor cells and thus its inhibition might slow the growth or spread of tumors.

[0091] "Treatment" of multiple sclerosis includes the various forms of the disease including relapsing-remitting, chronic progressive, etc., and the S1P receptor agonists can be used alone or in conjunction with other agents to relieve signs and symptoms of the disease as well as prophylactically.

[0092] In another aspect, the present invention provides compositions and methods for the use of the S1P analogs of the invention to prevent, inhibit, or treat neuropathic pain by agonizing or antagonizing the S1P receptors. Pain can be nociceptive or neuropathic in nature. Neuropathic pain is characterized by its chronic nature, an absence of an obvious, direct cause (*i.e.*, tissue damage), and allodynia. Allodynia is the perception of normal stimuli as painful (examples include the touch of clothing, warm or cool air, etc.). Neuropathic pain is often a sequel to nerve damage in an extremity such as an arm, or more often, a leg. Typically, neuropathic pain is not responsive to opiates or non-steroidal anti-inflammatory drugs such as aspirin.

[0093] In another aspect, the present invention provides compositions and methods for the use of S1P analogs to prevent and inhibit vascular restenosis following vascular injury. In one aspect, the injury can be due to balloon angioplasty. The present invention further provides methods for treating subjects to prevent vascular restenosis.

[0094] In another aspect, the present invention provides compositions and methods for the use of sphingosine analogs (including S1P pro-drugs) to prevent asthma attacks. In one aspect, the asthma could be due to over production of cysteinyl leukotrienes. The present invention further provides methods for treating subjects to treat asthma.

[0095] In another aspect, the present invention provides compositions and methods for the use of sphingosine analogs (including S1P pro-drugs) to treat obesity.

[0096] In another aspect, the present invention provides compositions and methods for the use of sphingosine analogs (including S1P pro-drugs) to normalize blood lipid composition. In one aspect, blood low density lipoprotein (LDL or 'bad cholesterol') levels could be lowered. In another aspect, blood triglyceride levels could be lowered.

[0097] In another aspect, the present invention provides compositions and methods for the use of S1P analogs and S1P pro-drugs for the prevention and treatment of arteriosclerosis.

[0098] In another aspect, the present invention provides compositions and methods for the use of S1P analogs and S1P pro-drugs for the treatment of neoplastic disease. In

one aspect, this treatment is effected by application of S1P receptor antagonists that are efficacious by virtue of their anti-angiogenic properties. In another aspect, the treatment is effected by administration of sphingosine analogs that inhibit the multiple substrate lipid kinase.

[0099] In another aspect, the present invention provides compositions and methods for the use of S1P analogs and S1P pro-drugs for the treatment of neurodegenerative diseases. In one aspect, the treatment is for senile dementia of the Alzheimers type.

[00100] The present invention is also includes pharmaceutical compositions comprising the disclosed compounds of the present invention. More particularly, such compounds can be Formulated as pharmaceutical compositions using standard pharmaceutically acceptable carriers, fillers, solubilizing agents and stabilizers known to those skilled in the art. For example, a pharmaceutical composition including a disclosed compound, analog, derivative, or modification thereof, as described herein, is used to administer the appropriate compound to a subject.

[00101] The compounds of the invention are useful for treating a disease or disorder including administering to a subject in need thereof of a therapeutically acceptable amount of a compound of Formula (I), or a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), and a pharmaceutically-acceptable carrier.

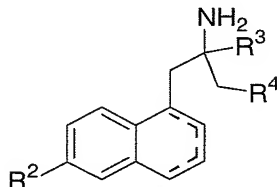
[00102] The disclosed compounds and method are directed to sphingosine 1-phosphate (S1P) analogs that have activity as receptor receptor agonists or antagonists at one or more S1P receptors, specifically the S1P₁, S1P₄ and S1P₅ receptor types. The disclosed compound and method include both compounds that have a phosphate moiety as well as compounds with hydrolysis-resistant phosphate surrogates such as phosphonates, *alpha*-substituted phosphonates particularly where the *alpha* substitution is a halogen and phosphothionates.

[00103] Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

[00104] Exemplary values for X¹, Y¹ and Z¹ are independently O, CH, CH₂, CHCF₃, N, NH, or S.

[00105] An additional exemplary value for X¹, Y¹ and Z¹ is CH₂.

[00106] An exemplary compound has the Formula



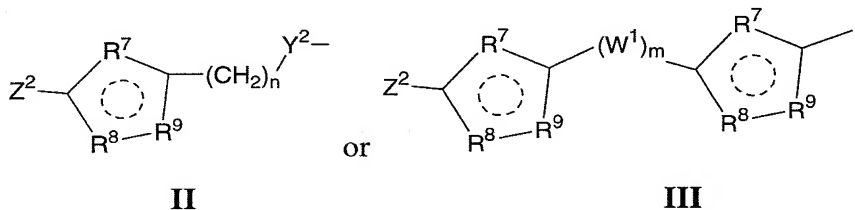
[00107] Exemplary values for R^1 include hydrogen, fluorine, chlorine, bromine, trifluoro-methyl, methoxy, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, or (C_1-C_6) alkyl substituted with, alkoxy or cyano.

[00108] More values for R^1 are hydrogen, trifluoro-methyl, or $-CH_2CF_3$.

[00109] Additional exemplary values for R^1 are alkyl-substituted aryl, aryl-substituted alkyl, or aryl-substituted arylalkyl.

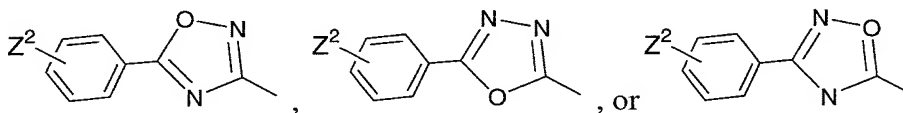
[00110] Even more exemplary values for R^1 are benzyl, phenylethyl, or benzyl substituted with methyl.

[00111] Exemplary values for R^2 include

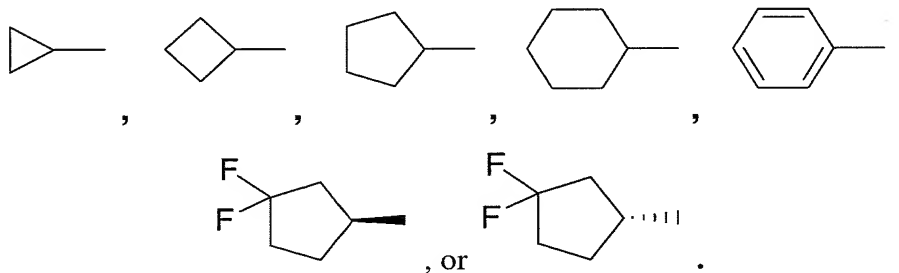


[00112] An exemplary value for W^1 is a bond, $-CH_2-CH_2-CH_2-$ or $-(C=O)(CH_2)_{1-5}$.

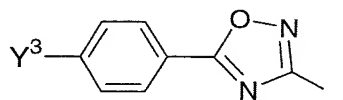
[00113] Additional for R^2 having Formula VI are



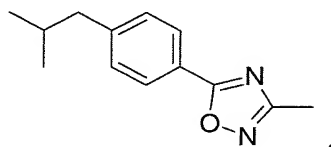
wherein Z^2 is $(CH_3)_3C-$, $CH_3CH_2(CH_3)_2C-$, $CH_3CH_2CH_2-$, $CH_3(CH_2)_2CH_2-$, $CH_3(CH_2)_4CH_2-$, $(CH_3)_2CHCH_2-$, $(CH_3)_3CCH_2-$, CH_3CH_2O- , $(CH_3)_2CHO-$, or $CF_3CH_2CH_2-$ or a group having the formula:



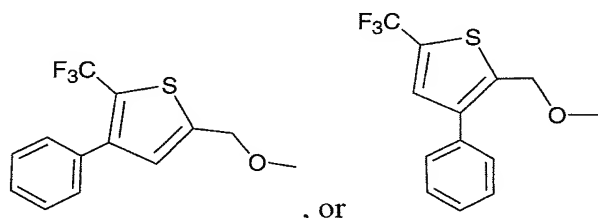
[00114] An additional value for an R^2 groups having Formula VI (*para* substituted 3,5-diphenyl-(1,2,4)-oxadiazoles) is;



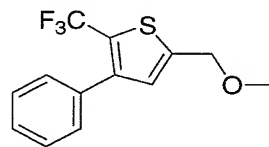
[00115] Another value for R^2 groups having Formula VI is;



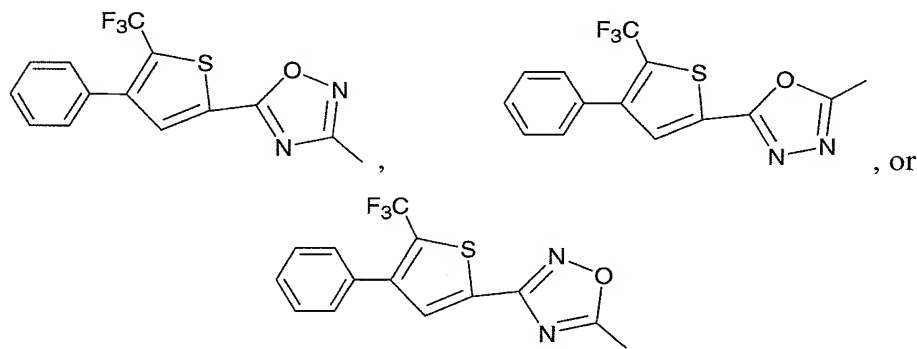
[00116] Another specific value for R^2 having Formula II is;



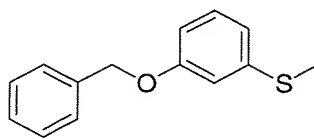
[00117] Another exemplary value for an R^2 group having Formula II is;



[00118] Additional values for R^2 groups having Formula III are;



[00119] Another value for R^2 having formula V is;



[00120] Additional exemplary values for R^2 include (C_1-C_{20}) alkyl, (C_1-C_{20}) alkoxy, or (C_2-C_{26}) alkoxyalkyl.

[00121] Additional exemplary values for R^2 include (C_1-C_{20}) alkyl, (C_1-C_{20}) alkoxy, or (C_2-C_{26}) alkoxyalkyl.

[00122] More exemplary values for R^2 include (C_1-C_{10}) alkyl, (C_2-C_{10}) alkenyl and (C_2-C_{10}) alkynyl or (C_1-C_{10}) alkoxy optionally substituted with carbonyl ($C=O$) or oxime ($C=NR^d$) groups.

[00123] Additional values for R^2 include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, trifluoromethyl, trifluoroethyl, trifluoromethoxy, trifluoroethoxy, methoxy, ethoxy, propoxy, butoxy, pentoxy, heptoxy, or octoxy.

[00124] Exemplary values for R^3 include methyl, hydroxymethyl, ethyl, hydroxyethyl, propyl, hydroxypropyl, or isopropyl.

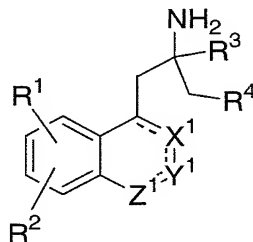
[00125] Additional values for R^3 are methyl, hydroxymethyl, ethyl, or hydroxyethyl.

[00126] Exemplary values for R^4 include is hydroxy, or phosphate ($-OPO_3H_2$).

Additional embodiments

[00127] Additional embodiments of the invention include:

1. A compound of Formula I:



wherein

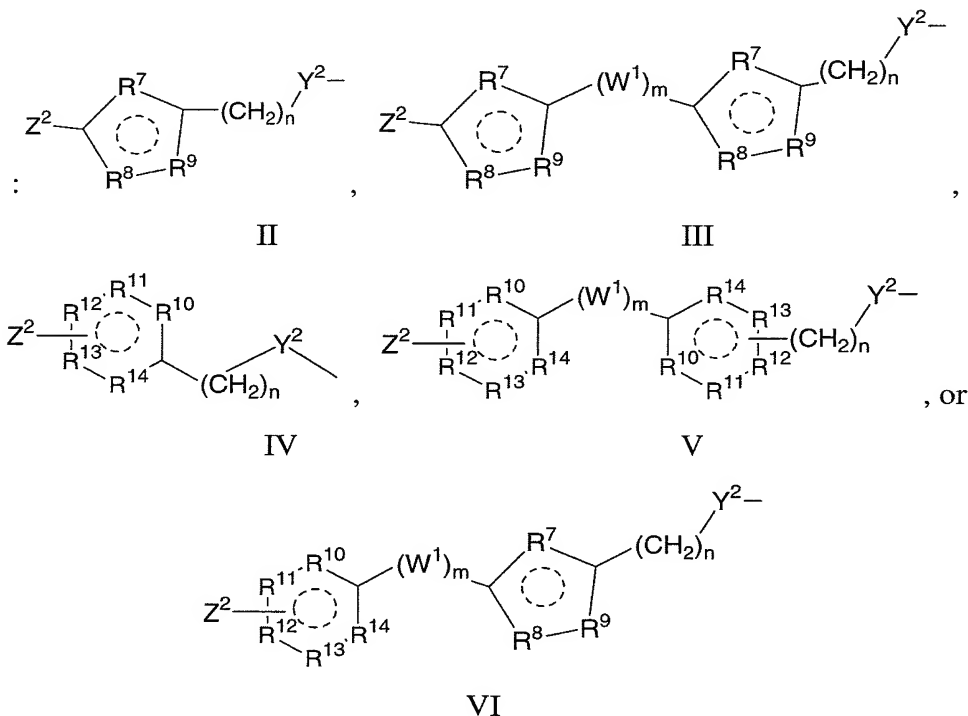
X^1 , Y^1 and Z^1 are independently O, CR^a , CR^aR^b , N, NR^c , or S;

R^1 and R^2 are independently hydrogen, halo, halo(C_1-C_{10})alkyl, cyano, $-NR^aR^b$, (C_1-C_{20}) alkyl, (C_2-C_{20}) alkenyl, (C_2-C_{20}) alkynyl, (C_1-C_{20}) alkoxy, (C_2-C_{26}) alkoxyalkyl, (C_3-C_{12}) cycloalkyl, (C_6-C_{10}) aryl, (C_7-C_{30}) arylalkyl, (C_2-C_{10}) heterocyclic, (C_4-C_{10}) heteroaryl, or (C_4-C_{10}) heteroaryl(C_1-C_{20})alkyl;

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclic, or heteroaryl groups of R^1 and R^2 independently are optionally perfluorinated or optionally substituted with 1, 2, 3, or 4 groups where the substituent groups are independently hydroxy, halo, cyano, (C_1-C_{10}) alkoxy, C_6 -aryl, (C_7-C_{24}) arylalkyl, oxo ($=O$), or imino ($=NR^d$), wherein one or more of the carbon atoms in the R^1 or R^2 alkyl groups can be independently replaced with non-peroxide oxygen,

sulfur or NR^c; the alkyl groups of R³ are optionally substituted with 1, or 2 hydroxy groups; or

R^2 can be a group having formula II, III, IV, V, or VI;



wherein each R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, and R¹⁴ is independently O, S, C, CR¹⁵, CR¹⁶R¹⁷, C=O, N or NR¹⁸;

each R¹⁵, R¹⁶ and R¹⁷ is independently hydrogen, halo, (C₁-C₁₀)alkyl, (C₆-C₁₀)aryl, (C₁-C₁₀)alkyl substituted with halo, hydroxy, (C₁-C₁₀)alkoxy, or cyano; and where R¹⁸ can be hydrogen or (C₁-C₁₀)alkyl;

where Z^2 is hydrogen, halo, halo(C_1 - C_{10})alkyl, cyano, $-NR^aR^b$, (C_1 - C_{20})alkyl, (C_2 - C_{20})alkenyl, (C_2 - C_{20})alkynyl, (C_1 - C_{20})alkoxy, (C_2 - C_{26})alkoxyalkyl, (C_3 - C_{12})cycloalkyl, (C_6 - C_{10})aryl, (C_7 - C_{30})arylalkyl, (C_2 - C_{10})heterocyclic, (C_4 - C_{10})heteroaryl, or (C_4 - C_{10})heteroaryl(C_1 - C_{20})alkyl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclic, or heteroaryl groups of Z^2 are optionally perfluorinated or optionally substituted with 1, 2, 3, or 4 groups where the substituent groups are independently hydroxy, halo, cyano, (C_1 - C_{10})alkoxy, C_6 -aryl, (C_7 - C_{24})arylalkyl, oxo ($=O$), or imino ($=NR^d$), wherein one or more of the carbon atoms in the Z^2 alkyl groups can be independently replaced with non-peroxide oxygen, sulfur or NR^c ;

○ indicates one or more optional double bonds;

wherein Y^2 is a bond, O, S, C=O, or NR^c , CH_2 ; W^1 is a bond, $-CH_2-$ and m is 1, 2, or 3, or $(C=O)(CH_2)_{1-5}$ and m is 1; wherein W^1 is optionally interrupted with non-peroxide O, S, C=O, or NR^c ;

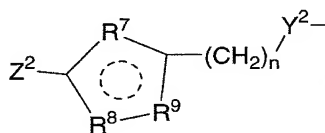
n is 0, 1, 2, or 3; each $---$ represents an optional double bond;

R^3 is hydrogen, (C_1-C_{10}) alkyl, hydroxy (C_1-C_{10}) alkyl or (C_1-C_{10}) alkoxy; and

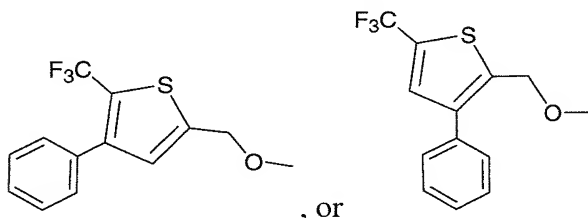
R^4 is hydroxyl ($-OH$), phosphate ($-OPO_3H_2$), phosphonate ($-CH_2PO_3H_2$), or α -substituted phosphonate;

each R^a , R^b , R^c , and R^d is independently hydrogen, or (C_1-C_{10}) alkyl; or a pharmaceutically acceptable salt or ester thereof.

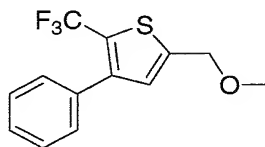
2. The compound of embodiment 1, wherein R^1 is hydrogen, fluorine, chlorine, bromine, trifluoro-methyl, methoxy, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_1-C_6) alkyl substituted with, alkoxy or cyano, alkyl-substituted aryl, aryl-substituted alkyl, or aryl-substituted arylalkyl.
3. The compound of embodiment 2, wherein R^1 is hydrogen, trifluoro-methyl, or $-CH_2CF_3$.
4. The compound of embodiment 2, wherein R^1 is benzyl, phenylethyl, or benzyl substituted with methyl.
5. The compound of any of embodiments 1-4, wherein R^2 is



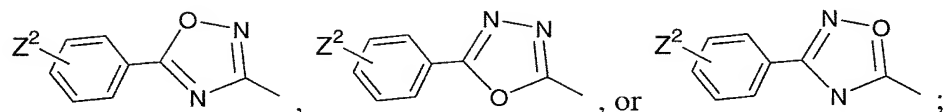
6. The compound of embodiment 5, wherein R^2 is:



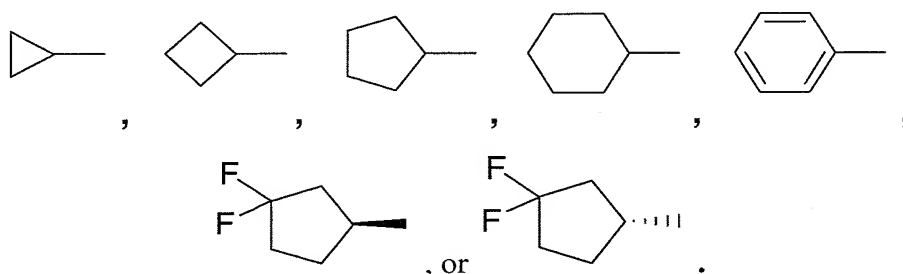
7. The compound of embodiment 6, wherein R^2 is



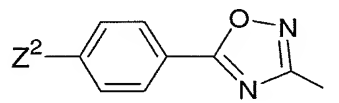
8. The compound of any of embodiments 1-4, wherein R^2 is:



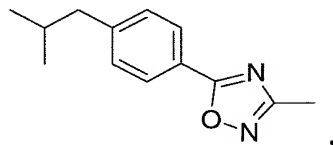
wherein Z^2 is $(CH_3)_3C-$, $CH_3CH_2(CH_3)_2C-$, $CH_3CH_2CH_2-$, $CH_3(CH_2)_2CH_2-$, $CH_3(CH_2)_4CH_2-$, $(CH_3)_2CHCH_2-$, $(CH_3)_3CCH_2-$, CH_3CH_2O- , $(CH_3)_2CHO-$, or $CF_3CH_2CH_2-$ or a group having the formula:



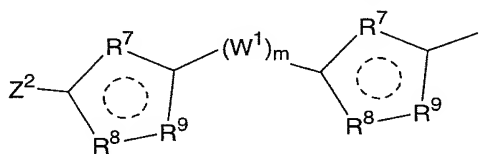
9. The compound of embodiment 8, wherein R^2 is:



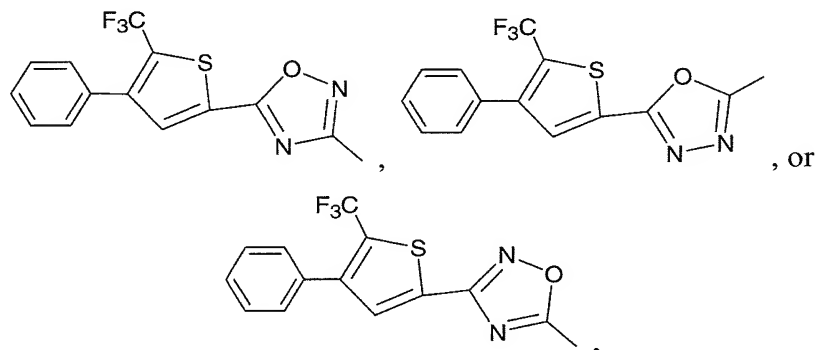
10. The compound of embodiment 9, wherein R^2 is:



11. The compound of any of embodiments 1-4, wherein R^2 is:

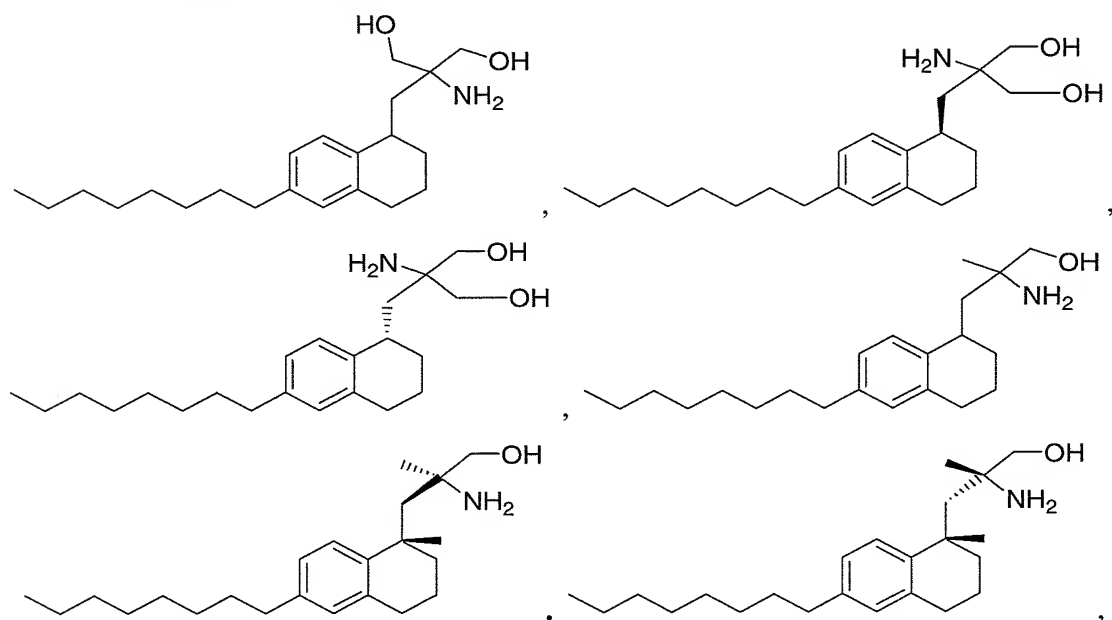


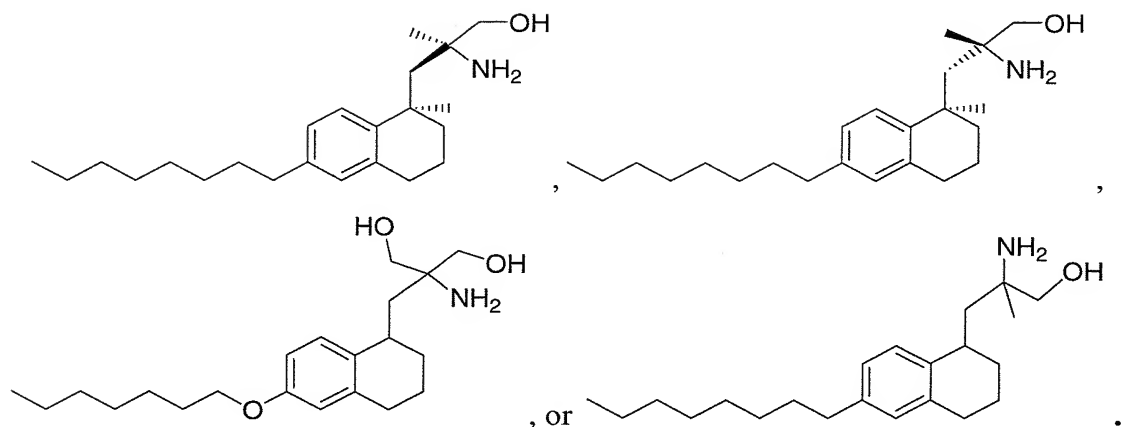
12. The compound of embodiment 11, wherein R^2 is



13. The compound of any of embodiments 1-4, wherein R^2 is (C_1-C_{20}) alkyl, or (C_1-C_{20}) alkoxy.

14. The compound of embodiment 13, wherein R^2 is (C_1-C_{10}) alkyl, (C_2-C_{10}) alkenyl and (C_2-C_{10}) alkynyl or (C_1-C_{10}) alkoxy optionally substituted with carbonyl ($C=O$) or oxime ($C=NR^d$) groups.
15. The compound of embodiment 14, wherein R^2 is methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, trifluoromethyl, trifluoroethyl, trifluoromethoxy, trifluoroethoxy, methoxy, ethoxy, propoxy, butoxy, pentoxy, heptoxy, or octoxy.
16. The compound of any of embodiments 1-15, wherein each of X^1 , Y^1 and Z^1 is CH_2 .
17. The compound of any of embodiments 1-16, wherein R^3 is hydrogen, methyl, hydroxymethyl, ethyl, hydroxyethyl, propyl, or isopropyl.
18. The compound of embodiment 17, wherein R^3 is hydrogen, methyl, hydroxymethyl, ethyl, or hydroxyethyl.
19. The compound of any of embodiments 1-18, having the Formula



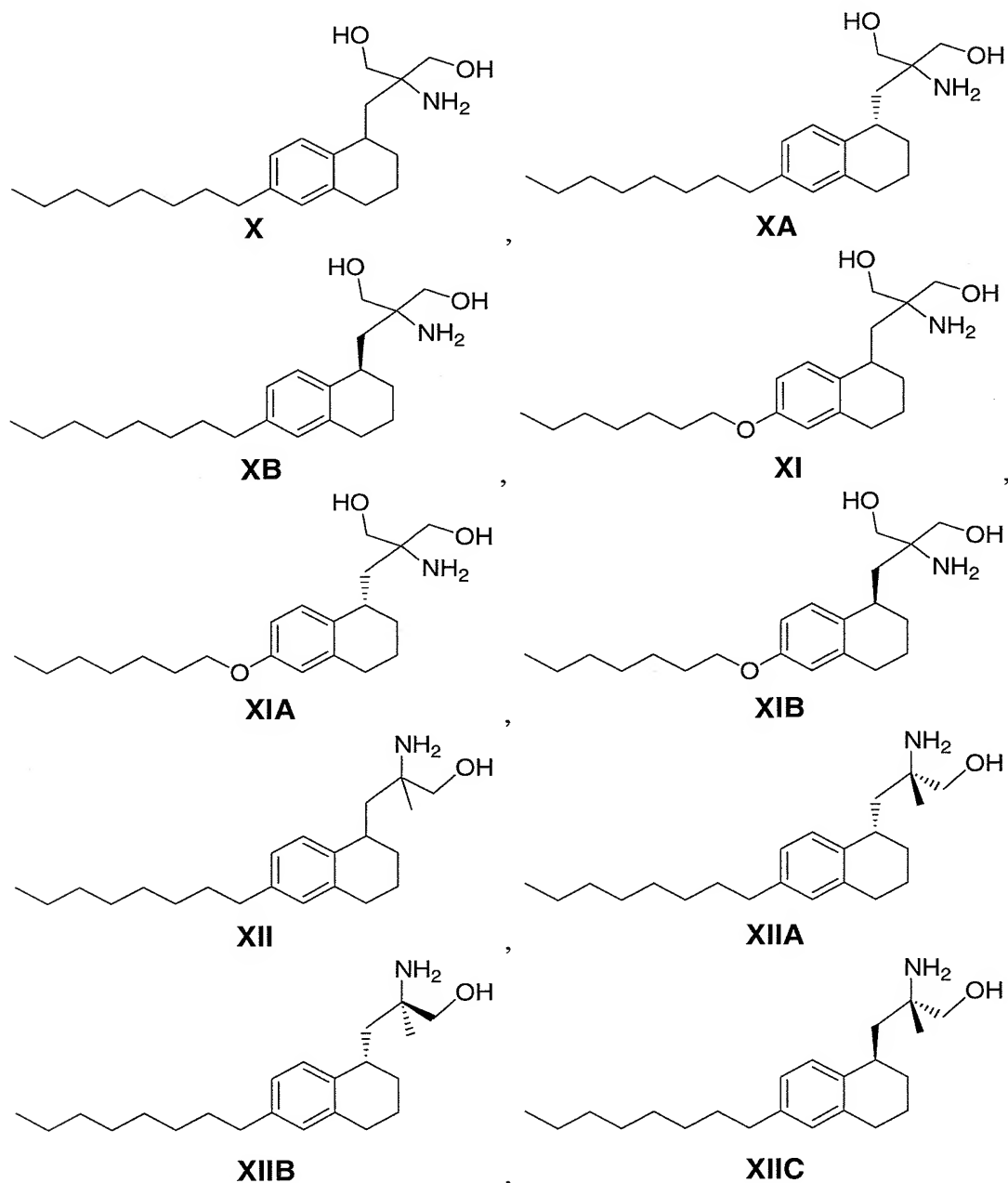


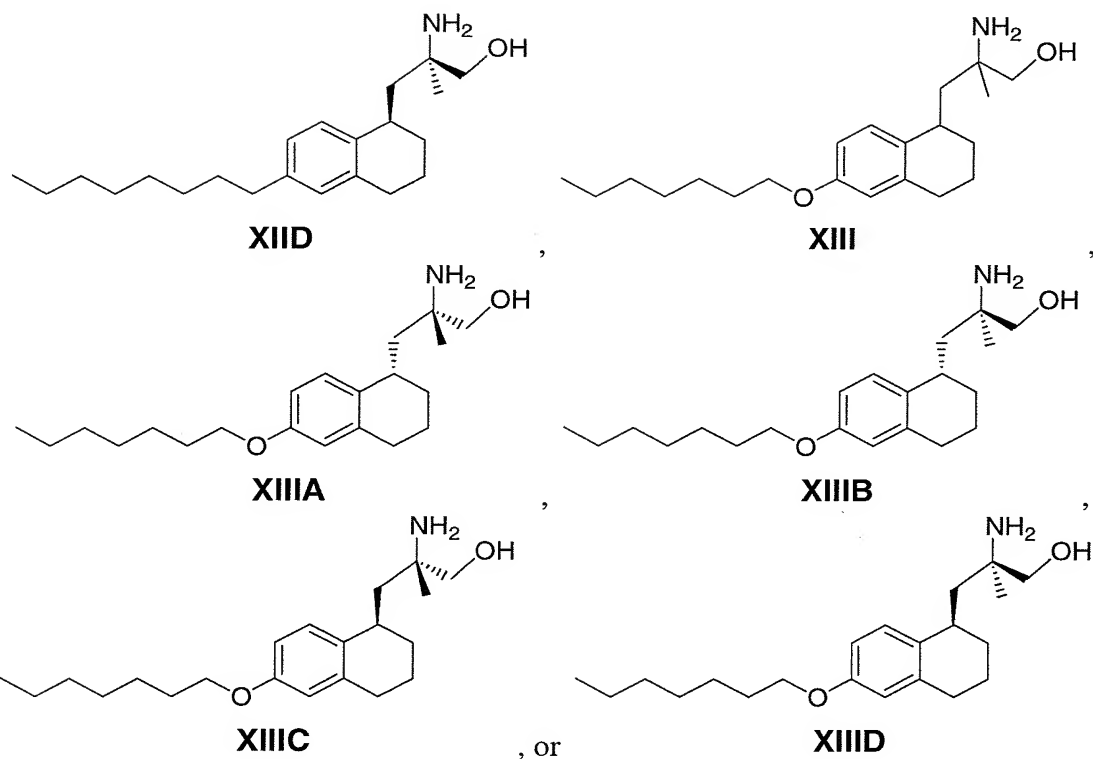
20. A method for prevention or treatment of a pathological condition or symptom in a mammal, wherein the activity of sphingosine 1-phosphate receptors is implicated and agonism of such activity is desired, comprising administering to said mammal an effective amount of a compound of any of embodiments 1-19.
21. The method of embodiment 19, wherein the pathological condition is an autoimmune disease.
22. The method of embodiment 21, wherein the autoimmune disease is uveitis, type I diabetes, rheumatoid arthritis, inflammatory bowel diseases, or multiple sclerosis.
23. The method of embodiment 22, wherein the autoimmune disease is multiple sclerosis.
24. The method of embodiment 23, wherein the pathological condition is altering lymphocyte trafficking.
25. The method of embodiment 24, wherein the treatment is altering of lymphocyte trafficking.
26. The method of embodiment 25, wherein lymphocyte trafficking provides prolonged allograft survival.
27. The method of embodiment 26, wherein the allograft is for transplantation.
28. A method for prevention or treatment of a pathological condition or symptom in a mammal, wherein the activity S1P lyase implicated and inhibition of the S1P lyase is desired, comprising administering to said mammal an effective amount of a compound of any of embodiments 1-19.
29. A compound of any of claims 1-19 for use in medical therapy.
30. Use of a compound of any of embodiments 1-19, to prepare a medicament useful for prevention or treatment of a pathological condition or symptom in a

mammal, wherein the activity of sphingosine 1-phosphate receptors is implicated.

31. The use of embodiment 30, wherein the medicament comprises a carrier.
32. The use of embodiment 31, wherein the carrier is a liquid.

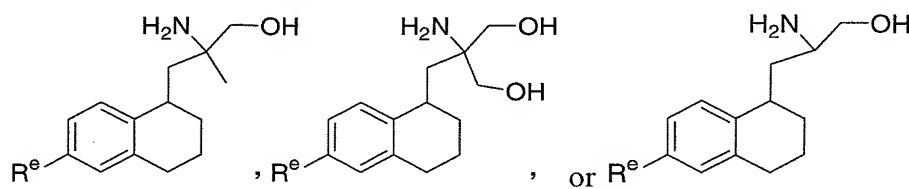
[00128] Exemplary compounds of the invention have Formulas





[00129] Additional compounds of Formula IA or IB are illustrated in table 1, below.

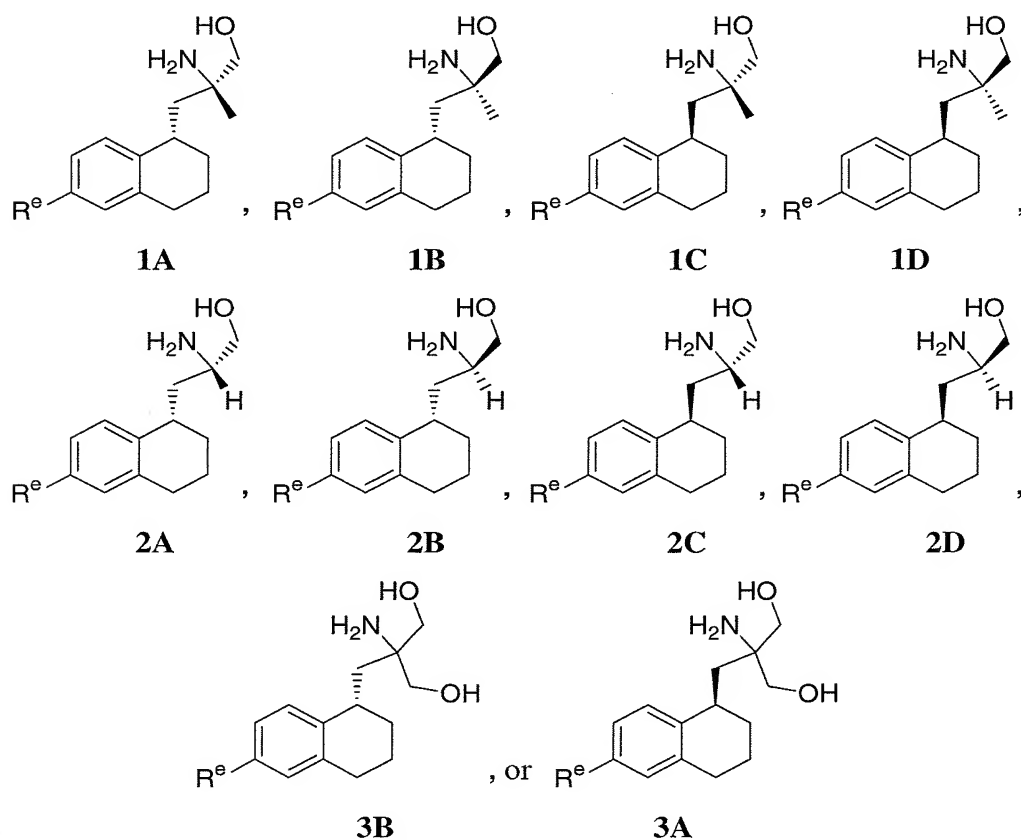
Table 1



Compound	R ^e
XX	
XXI	
XXII	

XXIII	
XXIV	
XXV	
XXXI	

[00130] The compounds having formulas **XX** through **XXV** or **XXXI** also include all enantiomers thereof such as:



where the compounds include each of the R^e groups from Table 1.

[00131] In another aspect, the invention provides S1P receptor pro-drug compounds having the general structure of Formula I, is provided by a compound with a mono-substituted tetralin ring system that has the structure (VIII). In some embodiments of structure (I), the compound (*e.g.*, X and XI) has only a single chiral center and that the amino carbon is pro-chiral, *i.e.*, will become chiral following enzyme-catalyzed phosphorylation.

[00132] Without wishing to be bound by any particular theory, it is expected that the compounds described herein are pro-drugs, *i.e.*, are activated by phosphorylation of the primary alcohol to form the mono-phosphorylated analog. Additionally, the active drugs are expected to be agonists at the S1P type 1 receptor.

[00133] In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, preparation and administration of the compounds as pharmaceutically salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α -ketoglutarate, and α -glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

[00134] Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

[00135] Pharmaceutically-acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases, include by way of example only, sodium, potassium, lithium, ammonium, calcium and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, such as alkyl amines, dialkyl amines, trialkyl amines, substituted alkyl amines, di(substituted alkyl) amines, tri(substituted alkyl) amines, alkenyl amines, dialkenyl amines, trialkenyl amines, substituted alkenyl amines, di(substituted alkenyl) amines, tri(substituted alkenyl) amines, cycloalkyl amines, di(cycloalkyl) amines, tri(cycloalkyl) amines, substituted cycloalkyl amines,

disubstituted cycloalkyl amine, trisubstituted cycloalkyl amines, cycloalkenyl amines, di(cycloalkenyl) amines, tri(cycloalkenyl) amines, substituted cycloalkenyl amines, disubstituted cycloalkenyl amine, trisubstituted cycloalkenyl amines, aryl amines, diaryl amines, triaryl amines, heteroaryl amines, diheteroaryl amines, triheteroaryl amines, heterocyclic amines, diheterocyclic amines, triheterocyclic amines, mixed di- and tri-amines where at least two of the substituents on the amine are different and are selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, and the like. Also included are amines where the two or three substituents, together with the amino nitrogen, form a heterocyclic or heteroaryl group. Examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like. It should also be understood that other carboxylic acid derivatives would be useful in the practice of this invention, for example, carboxylic acid amides, including carboxamides, lower alkyl carboxamides, dialkyl carboxamides, and the like.

[00136] The compounds of Formula I can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, *i.e.*, orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

[00137] Thus, the present compounds may be systemically administered, *e.g.*, orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least about 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage

form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

[00138] The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

[00139] The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[00140] The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be

maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

[00141] Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

[00142] For topical administration, the present compounds may be applied in pure form, *i.e.*, when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or Formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

[00143] Suitable solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

[00144] Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

[00145] Examples of useful dermatological compositions which can be used to deliver the compounds of Formula I to the skin are known to the art; for example, see

Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

[00146] Useful dosages of the compounds of Formula I can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

[00147] Generally, the concentration of the compound(s) of Formulas I-IV in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.

[00148] The amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

[00149] In general, however, a suitable dose will be in the range of from about 0.5 to about 100 mg/kg, *e.g.*, from about 10 to about 75 mg/kg of body weight per day, such as 3 to about 50 mg per kilogram body weight of the recipient per day, preferably in the range of 6 to 90 mg/kg/day, most preferably in the range of 15 to 60 mg/kg/day.

[00150] The compound is conveniently administered in unit dosage form; for example, containing 5 to 1000 mg, conveniently 10 to 750 mg, most conveniently, 50 to 500 mg of active ingredient per unit dosage form.

[00151] Ideally, the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.5 to about 75 μ M, preferably, about 1 to 50 μ M, most preferably, about 2 to about 30 μ M. This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the active ingredient, optionally in saline, or orally administered as a bolus containing about 1-100 mg of the active ingredient. Desirable blood levels may be maintained by continuous infusion to provide about 0.01-5.0 mg/kg/hr or by intermittent infusions containing about 0.4-15 mg/kg of the active ingredient(s).

[00152] The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four, or

more sub-doses per day. The sub-dose itself may be further divided, *e.g.*, into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

[00153] The method of the invention includes a kit comprising an inhibitor identified in the invention and an instructional material which describes administering the inhibitor or a composition comprising the inhibitor to a cell or a subject. This should be construed to include other embodiments of kits that are known to those skilled in the art, such as a kit comprising a (preferably sterile) solvent suitable for dissolving or suspending the composition of the invention prior to administering the compound to a cell or a subject. Preferably, the subject is a human.

[00154] The term “instructional material” includes a publication, a recording, a diagram, or any other medium of expression which can be used to communicate the usefulness of the composition of the invention for its designated use. The instructional material of the kit of the invention may, for example, be affixed to a container which contains the composition or be shipped together with a container which contains the composition. Alternatively, the instructional material may be shipped separately from the container with the intention that the instructional material and the composition be used cooperatively by the recipient.

[00155] In accordance with the present invention, as described above or as discussed in the Examples below, there can be employed conventional chemical, cellular, histochemical, biochemical, molecular biology, microbiology, and *in vivo* techniques which are known to those of skill in the art. Such techniques are explained fully in the literature.

[00156] Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention.

[00157] Processes for preparing compounds of Formula I or for preparing intermediates useful for preparing compounds of Formula I are provided as further embodiments of the invention. Intermediates useful for preparing compounds of Formula I are also provided as further embodiments of the invention. The processes are provided as further embodiments of the invention and are illustrated in the schemes herein wherein the meanings of the generic radicals are as given above unless otherwise qualified.

[00158] Processes for preparing compounds of Formula I or for preparing intermediates useful for preparing compounds of Formula I are provided as further embodiments of the invention. Intermediates useful for preparing compounds of Formula I are also provided as further embodiments of the invention. The compounds of the invention can be prepared using starting materials and methods known in the art.

[00159] The syntheses of target molecules are illustrated in Scheme 1, Scheme 2, and Scheme 3 (See **Figs. 3-5**).

[00160] The invention is now described with reference to the following Examples and Embodiments. Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the disclosed compounds. The following working examples therefore, are provided for the purpose of illustration only, point out the preferred embodiments, and are not to be construed as limiting in any way the remainder of the disclosure. Therefore, the examples should be construed to encompass any and all variations which become evident as a result of the teaching provided herein.

Scheme 1:

Example 1: Compound 2

[00161] 6-Hydroxy-2-tetralone (4.0 g, 24.7 mmol) is dissolved in methylene chloride (50 mL) and cooled to 0° C under inert atmosphere. Trifluoromethyl sulfonyl anhydride (5.55 g, 25.0 mmol) is added to the reaction. 2,6-Lutidine (3.2 g, 30 mmol) is introduced dropwise over 10 minutes and the reaction is stirred at 0° C for an additional 2 hours. The reaction volume is reduced to about 10 mL *in vacuo* and filtered to remove insoluble material. The filter cake is washed with ether (2 X 25 mL), the organic layers combined and solvent removed *in vacuo* leaving a thick residue that is utilized in the next step without further purification.

Example 2: Compound 3

[00162] An octyl boronate intermediate is first generated by adding 1-octene (3.95 g, 36.0 mmol) to a solution of 9-BBN in THF (80.6 mL of a 0.5 M solution, 40.3 mmol). The reaction is stirred at room temperature overnight, then an aqueous solution of sodium hydroxide (7.0 mL of a 3.0 M solution) is added, followed by the addition of the crude residue (compound 2) from Example 1 dissolved in THF (25 mL) and Pd[P(Ph)₃]₄ (0.900 g, 0.785 mmol). The reaction is brought to reflux and maintained

for 12 hours under an inert atmosphere. The reaction is then cooled, filtered, concentrated *in vacuo* and the residue purified using silica gel chromatography with hexanes/ethyl acetate (75:25) as solvent. Purified 6-octyl-2-tetralone is a clear liquid (4.13 g, 16.1 mmol, 63%).

Example 3: Compound 3 (Alternate Route).

[00163] An octyl boronate intermediate is first generated by adding 1-octene (1.38 g, 14.1 mmol) to a solution of 9-BBN in THF (28.3 mL of a 0.5 M solution, 14.1 mmol). The reaction is stirred at room temperature overnight, then an aqueous solution of sodium hydroxide (5.0 mL of a 3.0 M solution) is added, followed by the addition of 6-bromo-2-tetralone (2.40 g, 10.0 mmol) and Pd[P(Ph)₃]₄ (0.310 g, 0.270 mmol). The reaction is brought to reflux and maintained for 12 hours under an inert atmosphere. The reaction is then cooled, filtered, concentrated *in vacuo* and the residue purified using silica gel chromatography with hexanes/ethyl acetate (75:25) as solvent to provide 6-octyl-2-tetralone (2.35 g, 8.5 mmol, 85%) as a clear liquid.

Example 4: Compound 4

[00164] Potassium hydride (1.07 g of a 30% w/w suspension in mineral oil, 8.0 mmol) is washed several times with pentane to remove the mineral oil, then THF (25 mL) is added and the mixture cooled to -40° C. 6-Octyl-2-tetralone (1.95 g, 7.0 mmol) dissolved in THF (20 mL) is added dropwise over 30 minutes at -40° C. The reaction is allowed to warm to 0° C for 30 minutes, then returned to -40° C. 2,2-Dimethyl-5-formyl-1,3-dioxan-5-yl)acetamide (1.65 g, 8.2 mmol) in THF (20 mL) is added dropwise and the reaction maintained at -40° C for 2 hours. The reaction is quenched by the addition of acetic anhydride (1.02 g, 10 mmol) at -40° C followed by warming the reaction to room temperature and stirring for 30 minutes. *P*-toluenesulfonic acid (~10 mg) is added and the reaction brought to reflux and maintained for 1 hour. The reaction is cooled partitioned between ether (200 mL) and aqueous sodium bicarbonate (5% w/w, 100 mL). The organic layer is removed, washed with aqueous bicarbonate (1 X 50 mL), then dried and the solvents removed *in vacuo*. The residue is purified using silica gel chromatography with hexanes (60%)-ethyl acetate (40%) to afford compound 4.

Example 5: Compound 5

[00165] Compound 4 (658 mg, 1.42 mmol) is dissolved in ethanol (15 mL). Palladium on activated carbon (90 mg of 10 wt. %) is added, the mixture is cooled to 0°C and a hydrogen atmosphere is introduced. The reaction is stirred vigorously overnight at 0°C, then filtered through Celite and the solvent removed *in vacuo*. Compound 5 is purified using chromatography on silica gel using hexanes (60%)-ethyl acetate (40%).

Example 6: Compound 6

[00166] Compound 5 (298 mg, 0.64 mmol) is dissolved in ethanol (10 mL) and sodium borohydride (10 mg) is added. The reaction mixture is stirred at room temperature for 3 hours. The mixture is partitioned between ether (30 mL) and water (10 mL). The organic layer is washed once with water (1 X 10 mL), then brine and dried over MgSO₄. The combined organic layers are removed *in vacuo* and the residue, containing the product isomeric alcohols (compound 6), is used in the next step without purification.

Example 7: Compound 7

[00167] The crude compound 6 is dissolved in toluene (10 mL) containing *p*-toluenesulfonic acid (~5 mg) containing activated 3A molecular sieve spheres (25 mg). The reaction is heated to 70° C under an inert atmosphere for 4 hours, cooled, filtered and partitioned between ether (25 mL) and aqueous sodium bicarbonate (5% w/w, 10 mL). The organic layer is washed once with aqueous bicarbonate solution (10 mL), then with brine and dried over MgSO₄. The solvents are removed *in vacuo* and the residue is purified by chromatography on silica gel using hexanes (50%)-ethyl acetate (50%).

Example 8: Compound 8

[00168] Compound 7 (138 mg, 0.29 mmol) is dissolved in ethanol (10 mL) and palladium on activated carbon (30 mg of 10 wt. %) is added. The reaction is maintained at room temperature, and a hydrogen atmosphere is introduced. The reaction is stirred vigorously overnight and then filtered through Celite. Aqueous hydrochloric acid (1.0 mL of a 5 N solution) is introduced and the reaction refluxed for 3 hours. The reaction is partitioned between ether (30 mL) and aqueous sodium bicarbonate solution (5% w/w, 10 mL). The organic layer is washed with aqueous

bicarbonate (1 X 10 mL), then with brine and dried over MgSO₄. The solvent removed *in vacuo*. Compound 8 is purified using chromatography on silica gel using hexanes (30%)-ethyl acetate (70%).

Example 9: Compound 9

[00169] Compound 8 (93 mg, 0.23 mmol) is dissolved in methanol (3.0 mL) and LiOH (100 mg, 1.54 mmol) is added. The reaction is heated at reflux for 2 hours, then partitioned between methylene chloride (10 mL) and water (5 mL). The aqueous layer is extracted with methylene chloride (2 X 5 mL) and the combined organics are then dried over MgSO₄. The organic layer is evaporated to dryness. The residue is purified using silica gel chromatography with methanol (25%)-methylene chloride (75%) to furnish compound 9.

Example 10: Compound 10

[00170] Compound 7 (See: Figure 3, Scheme 1) (100 mg, 0.21 mmol) is dissolved in ethanol (10 mL), aqueous hydrochloric acid (1.0 mL of a 5 N solution) is introduced and the reaction refluxed for 6 hours. The reaction is cooled, then partitioned between ether (30 mL) and aqueous sodium bicarbonate solution (5% w/w, 10 mL). The organic layer is separated, then washed with aqueous bicarbonate (1 X 10 mL), and brine, dried over MgSO₄, and the solvent removed *in vacuo*. Compound 10 is provided with chromatography on silica gel using hexanes (30%)-ethyl acetate (70%).

Example 11: Compound 11

[00171] Compound 10 (69 mg, 0.17 mmol) is dissolved in methanol (3.0 mL) and LiOH (100 mg, 1.54 mmol) is added. The reaction is heated at reflux for 2 hours, partitioned between methylene chloride (10 mL) and water (5 mL). The aqueous layer is extracted with methylene chloride (2 X 5 mL) and the combined organics are then dried over MgSO₄. The organic layer is evaporated to dryness. The residue is purified using silica gel chromatography with methanol (25%)-methylene chloride (75%) to give compound 11.

[00172] The assays below are standard literature reported assays known in the art for confirming and quantifying the activity of the disclosed compounds.

Example 12: Sphingosine Kinase Assay

[00173] Recombinant sphingosine kinase type 2 (SPHK2) is prepared by forcing the expression of the mouse or human recombinant enzyme by transfecting the relevant

plasmid DNA into HEK293T or CHO K1 cells. After about 60 hours, cells are harvested, broken and the non-microsomal (*e.g.*, soluble) fraction is retained. The broken cell supernatant fluid containing the recombinant enzyme is mixed with test compounds (*e.g.*, FTY720, AA151, VIII and XVIII) (5 – 50 micromolar) and γ -32P-ATP and incubated for 0.5 – 2.0 hours at 37°C. The lipids in the reaction mixture are extracted into an organic solvent and displayed by normal phase thin layer chromatography. The radio-labeled bands are detected by autoradiography, scraped from the plate and quantified by scintillation counting. The test compounds are used at a concentration of about 50 μ M, incubation time is about 20 minutes.

Example 13: GTP γ S-35 binding Assay

[00174] This assay illustrates agonist activation of G protein coupled receptors (GPCRs) in isolation. The assay forces expression concomitantly of a recombinant GPCR (*e.g.*, the S1P1-5 receptor) and each of the three subunits (*e.g.*, α -i2, β -1, and γ -2) of a heterotrimeric G protein in a HEK293T cell by transfecting the cell with four plasmid DNAs encoding the respective proteins. About 60 hours after transfection cells are harvested, broken, the nucleus discarded, and the crude microsomes are prepared from the remainder. Agonist (*e.g.*, S1P) stimulation of the receptor-G protein complex on the microsomes results in the exchange of GTP for GDP on the α -subunit in a dose-dependent manner. The GTP-bound α -subunit is detected using a GTP analog (GTP γ S-35), which is a radionuclide (sulfur-35) labeled phosphothionate that is not hydrolyzed to GDP. The microsomes with the adherent G proteins are collected by filtration and the bound GTP γ S-35 quantified in a liquid scintillation counter. The assay provides relative potency (EC₅₀ values) and maximum effect (efficacy, E_{max}). Antagonist activity is detected as rightward shifts in the agonist dose-response curve in the presence of a fixed amount of antagonist. If the antagonist behaves competitively, the affinity of the receptor/antagonist pair (K_i) can be determined. The assay is described in Davis, M.D., J.J. Clemens, T.L. Macdonald and K.R. Lynch (2005) "S1P Analogs as Receptor Antagonists" Journal of Biological Chemistry, vol. 280, pp. 9833-9841.

Example 14: Lymphopenia Assay

[00175] The test compounds (*e.g.*, primary alcohols) are dissolved in 2% hydroxypropyl beta-cyclodextrin and introduced into groups of mice by oral gavage at

doses from .01, 1.0 and 10 mg/kg body weight. At intervals, *e.g.*, 24 hours, 48 hours, or 96 hours the mice are lightly anesthetized and *ca.* 0.1 mL of blood is drawn from the orbital sinus. The number of lymphocytes (in thousands per microliter of blood; normal is 4-11) is determined using a Hemavet blood analyzer.

Example 15: Heart Rate Assay

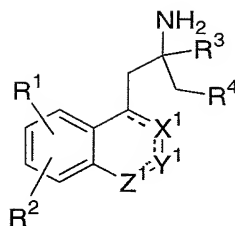
[00176] Mice are dosed with test compounds (intravenous, 3 mg/kg) or vehicle (2% hydroxypropyl beta-cyclodextrin) and the heart rate measured at 1 hour post dosing. Heart rate is captured in unrestrained, conscious animals using the ECGenie™ system.

[00177] The abbreviations used herein have their conventional meaning within the clinical, chemical, and biological arts. In the case of any inconsistencies, the present disclosure, including any definitions therein will prevail.

[00178] The disclosures of each and every patent, patent application, and publication cited herein are expressly incorporated herein by reference in their entirety into this disclosure. Illustrative embodiments of this disclosure are discussed and reference has been made to possible variations within the scope of this disclosure. These and other variations and modifications in the disclosure will be apparent to those skilled in the art without departing from the scope of the disclosure, and it should be understood that this disclosure and the claims shown below are not limited to the illustrative embodiments set forth herein.

We Claim

1. A compound of Formula I:



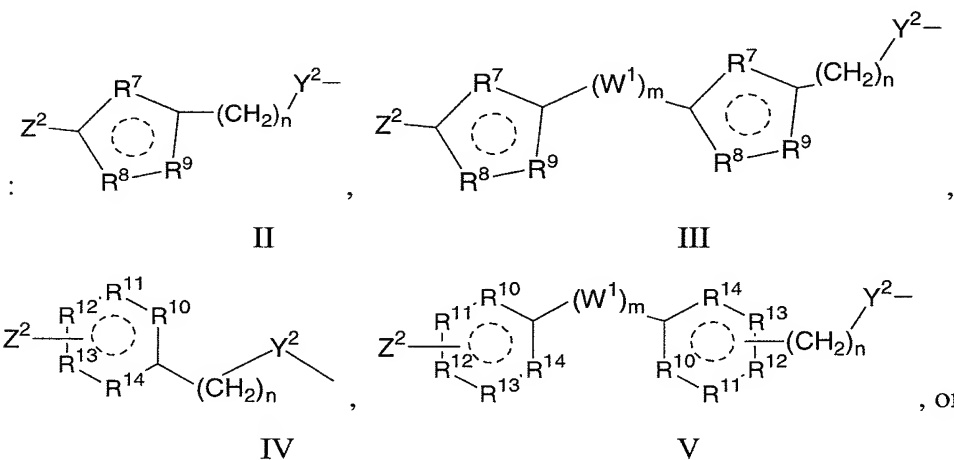
wherein

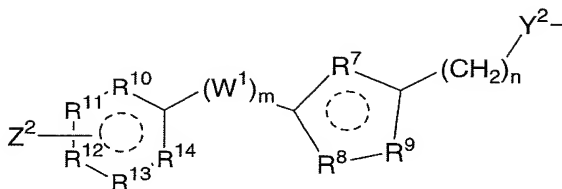
X¹, Y¹ and Z¹ are independently O, CR^a, CR^aR^b, N, NR^c, or S;

R¹ and R² are independently hydrogen, halo, halo(C₁-C₁₀)alkyl, cyano, -NR^aR^b, (C₁-C₂₀)alkyl, (C₂-C₂₀)alkenyl, (C₂-C₂₀)alkynyl, (C₁-C₂₀)alkoxy, (C₂-C₂₆)alkoxyalkyl, (C₃-C₁₂)cycloalkyl, (C₆-C₁₀)aryl, (C₇-C₃₀)arylalkyl, (C₂-C₁₀)heterocyclic, (C₄-C₁₀)heteroaryl, or (C₄-C₁₀)heteroaryl(C₁-C₂₀)alkyl;

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclic, or heteroaryl groups of R¹ and R² independently are optionally perfluorinated or optionally substituted with 1, 2, 3, or 4 groups where the substituent groups are independently hydroxy, halo, cyano, (C₁-C₁₀)alkoxy, C₆-aryl, (C₇-C₂₄)arylalkyl, oxo (=O), or imino (=NR^d), wherein one or more of the carbon atoms in the R¹ or R² alkyl groups can be independently replaced with non-peroxide oxygen, sulfur or NR^c; the alkyl groups of R³ are optionally substituted with 1, or 2 hydroxy groups; or

R^2 can be a group having formula II, III, IV, V, or VI;





VI

wherein each R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} is independently O, S, C, CR^{15} , $CR^{16}R^{17}$, C=O, N or NR^{18} ;

each R^{15} , R^{16} and R^{17} is independently hydrogen, halo, (C_1-C_{10}) alkyl, (C_6-C_{10}) aryl, (C_1-C_{10}) alkyl substituted with halo, hydroxy, (C_1-C_{10}) alkoxy, or cyano; and where R^{18} can be hydrogen or (C_1-C_{10}) alkyl;

wherein Z^2 is hydrogen, halo, halo (C_1-C_{10}) alkyl, cyano, $-NR^aR^b$, (C_1-C_{20}) alkyl, (C_2-C_{20}) alkenyl, (C_2-C_{20}) alkynyl, (C_1-C_{20}) alkoxy, (C_2-C_{26}) -alkoxyalkyl, (C_3-C_{12}) cycloalkyl, (C_6-C_{10}) aryl, (C_7-C_{30}) arylalkyl, (C_2-C_{10}) -heterocyclic, (C_4-C_{10}) heteroaryl, or (C_4-C_{10}) heteroaryl (C_1-C_{20}) alkyl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclic, or heteroaryl groups of Z^2 are optionally perfluorinated or optionally substituted with 1, 2, 3, or 4 groups where the substituent groups are independently hydroxy, halo, cyano, (C_1-C_{10}) alkoxy, C_6 -aryl, (C_7-C_{24}) arylalkyl, oxo (=O), or imino (=NR^d), wherein one or more of the carbon atoms in the Z^2 alkyl groups can be independently replaced with non-peroxide oxygen, sulfur or NR^c;

○ indicates one or more optional double bonds;

wherein Y^2 is a bond, O, S, C=O, or NR^c, CH_2 ; W^1 is a bond, $-CH_2-$ and m is 1, 2, or 3, or $(C=O)(CH_2)_{1-5}$ and m is 1; wherein W^1 is optionally interrupted with non-peroxide O, S, C=O, or NR^c;

n is 0, 1, 2, or 3; each --- represents an optional double bond;

R^3 is hydrogen, (C_1-C_{10}) alkyl, hydroxy (C_1-C_{10}) alkyl or (C_1-C_{10}) alkoxy;

and

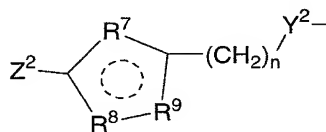
R^4 is hydroxyl ($-OH$), phosphate ($-OPO_3H_2$), phosphonate ($-CH_2PO_3H_2$), or α -substituted phosphonate;

each R^a , R^b , R^c , and R^d is independently hydrogen, or (C_1-C_{10}) alkyl; or a pharmaceutically acceptable salt or ester thereof.

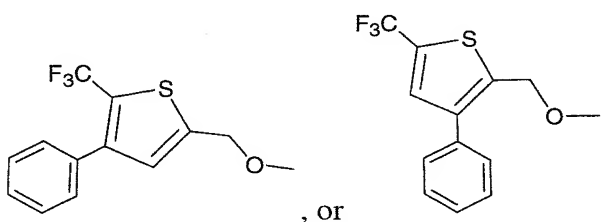
- The compound of claim 1, wherein R^1 is hydrogen, fluorine, chlorine, bromine, trifluoro-methyl, methoxy, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, $(C_1-$

C₆)alkyl substituted with, alkoxy or cyano, alkyl-substituted aryl, aryl-substituted alkyl, or aryl-substituted arylalkyl.

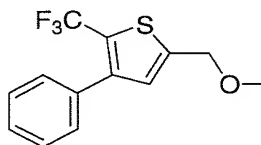
3. The compound of claim 2, wherein R¹ is hydrogen, trifluoro-methyl, or -CH₂CF₃.
4. The compound of claim 2, wherein R¹ is benzyl, phenylethyl, or benzyl substituted with methyl.
5. The compound of any of claims 1-4 wherein R² is



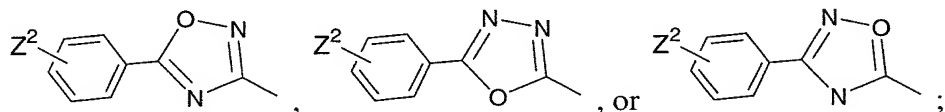
6. The compound of claim 5, wherein R² is:



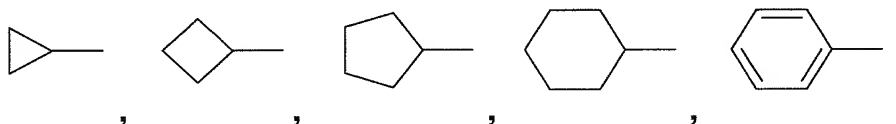
7. The compound of claim 6, wherein R² is

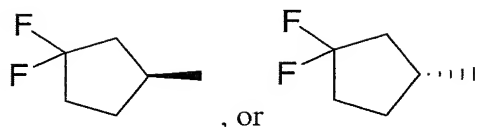


8. The compound of any of claims 1-4, wherein R² is:

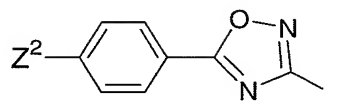


wherein Z² is (CH₃)₃C-, CH₃CH₂(CH₃)₂C-, CH₃CH₂CH₂-, CH₃(CH₂)₂CH₂-, CH₃(CH₂)₄CH₂-, (CH₃)₂CHCH₂-, (CH₃)₃CCH₂-, CH₃CH₂O-, (CH₃)₂CHO-, or CF₃CH₂CH₂- or a group having the formula:.

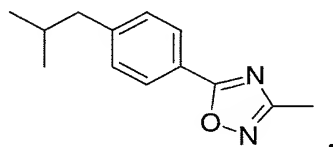




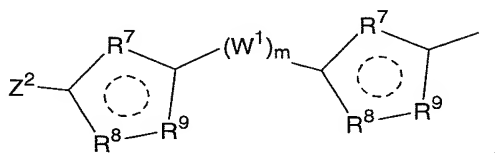
9. The compound of claim 8, wherein R^2 is:



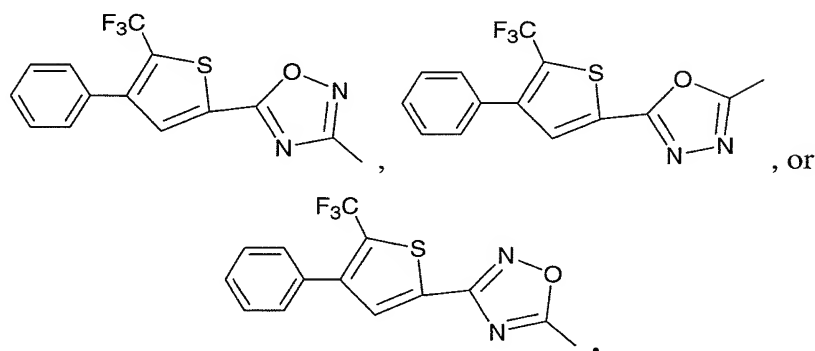
10. The compound of claim 9, wherein R^2 is:



11. The compound of any of claims 1-4, wherein R^2 is:



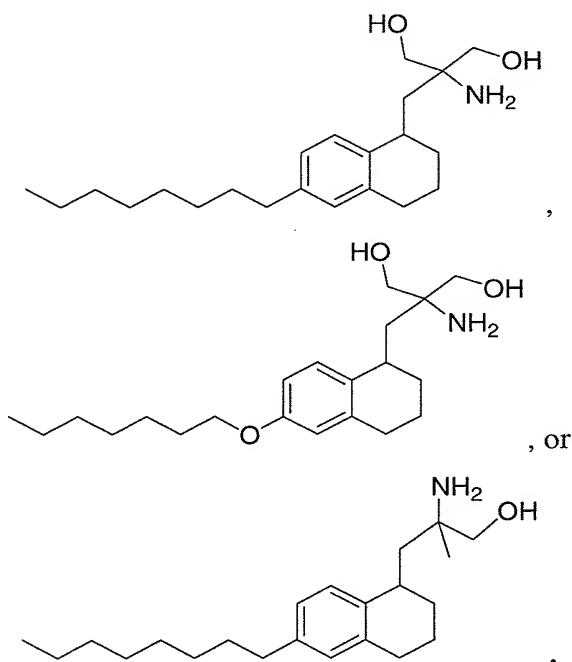
12. The compound of claim 11, wherein R^2 is



13. The compound of any of claims 1-4, wherein R^2 is (C_1-C_{20}) alkyl, or (C_1-C_{20}) alkoxy.
14. The compound of claim 13, wherein R^2 is (C_1-C_{10}) alkyl, (C_2-C_{10}) alkenyl and (C_2-C_{10}) alkynyl or (C_1-C_{10}) alkoxy optionally substituted with carbonyl ($C=O$) or oxime ($C=NR^d$) groups.
15. The compound of claim 14, wherein R^2 is methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, trifluoromethyl, trifluoroethyl, trifluoromethoxy,

trifluoroethoxy, methoxy, ethoxy, propoxy, butoxy, pentoxy, heptoxy, or octoxy.

16. The compound of any of claims 1-15, wherein X^1 , Y^1 and Z^1 are CH_2 .
17. The compound of any of claims 1-16, wherein R^3 is hydrogen, methyl, hydroxymethyl, ethyl, hydroxyethyl, propyl, or isopropyl.
18. The compound of claim 17, wherein R^3 is hydrogen, methyl, hydroxymethyl, ethyl, or hydroxyethyl.
19. The compound of any of claims 1-18, having the Formula



20. A method for prevention or treatment of a pathological condition or symptom in a mammal, wherein the activity of sphingosine 1-phosphate receptors is implicated and agonism of such activity is desired, comprising administering to said mammal an effective amount of a compound of any of claims 1-19.
21. The method of claim 20, wherein the pathological condition is an autoimmune disease.
22. The method of claim 21, wherein the autoimmune disease is uveitis, type I diabetes, rheumatoid arthritis, inflammatory bowel diseases, or multiple sclerosis.

23. The method of claim 22, wherein the autoimmune disease is multiple sclerosis.
24. The method of claim 23, wherein the pathological condition is altering lymphocyte trafficking.
25. The method of claim 24, wherein the treatment is altering of lymphocyte trafficking.
26. The method of claim 25, wherein lymphocyte trafficking provides prolonged allograft survival.
27. The method of claim 26, wherein the allograft is for transplantation.
28. A method for prevention or treatment of a pathological condition or symptom in a mammal, wherein the activity S1P lyase implicated and inhibition of the S1P lyase is desired, comprising administering to said mammal an effective amount of a compound of any of claims 1-19.
29. A compound of any of claims 1-19 for use in medical therapy.
30. Use of a compound of any of claims 1-19 to prepare a medicament useful for prevention or treatment of a pathological condition or symptom in a mammal, wherein the activity of sphingosine 1-phosphate receptors is implicated.
31. The use of claim 30, wherein the medicament comprises a carrier.
32. The use of claim 31, wherein the carrier is a liquid.

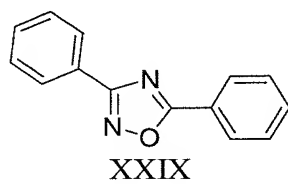
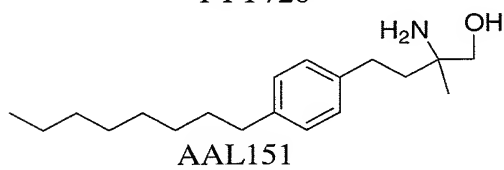
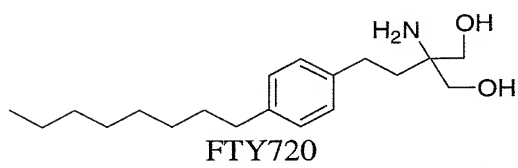
Fig. 1

FIG. 2A

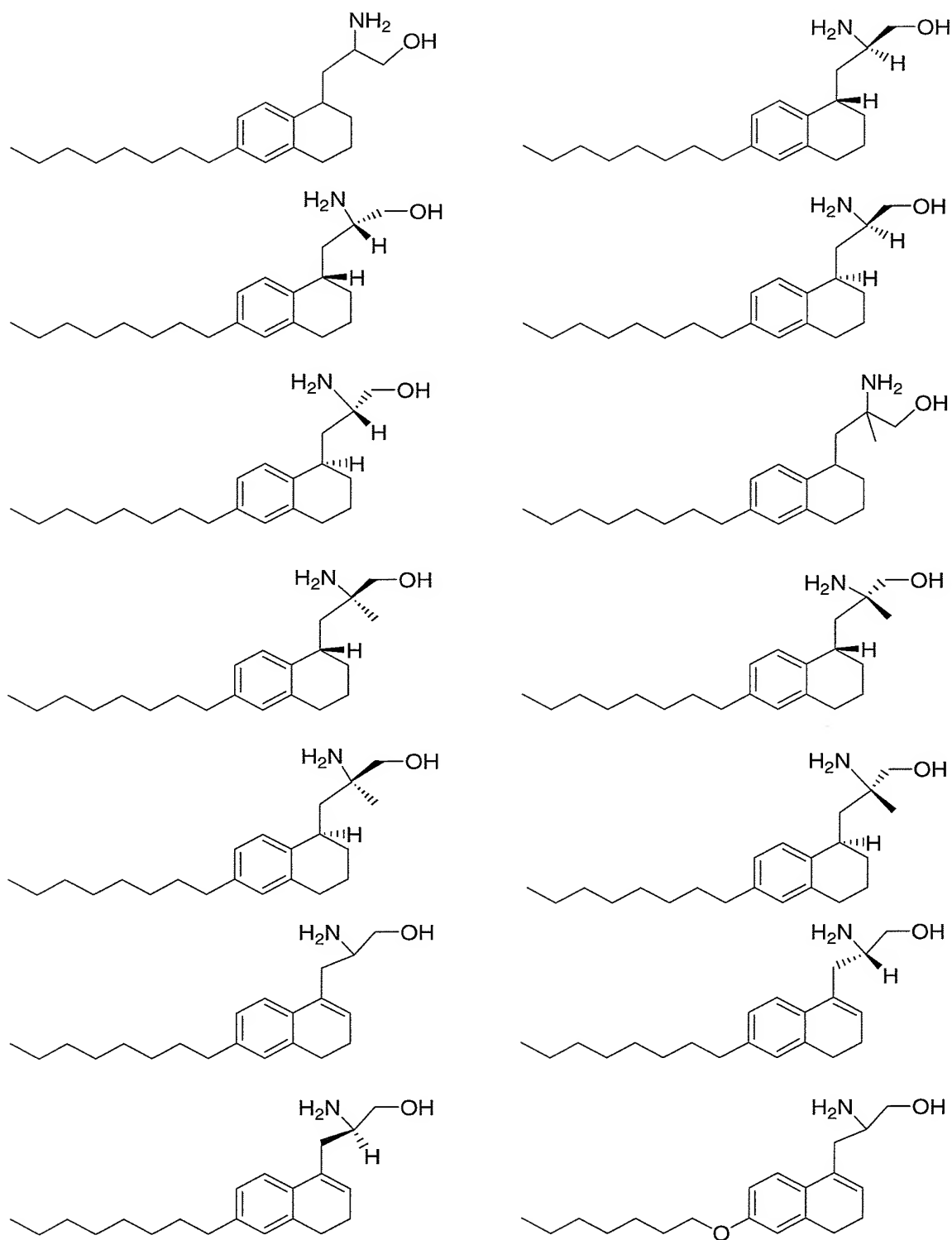


FIG. 2B

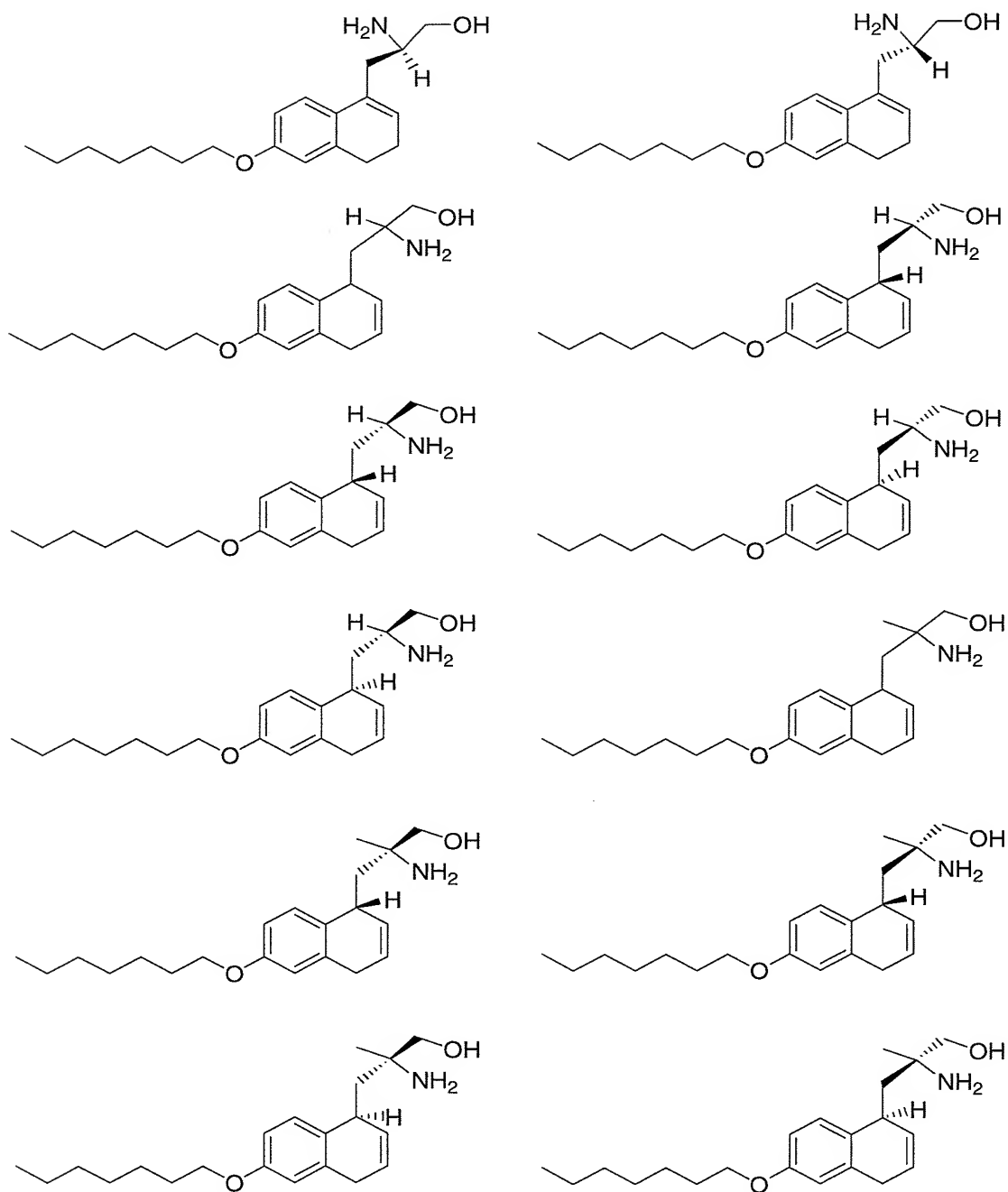


FIG. 2C

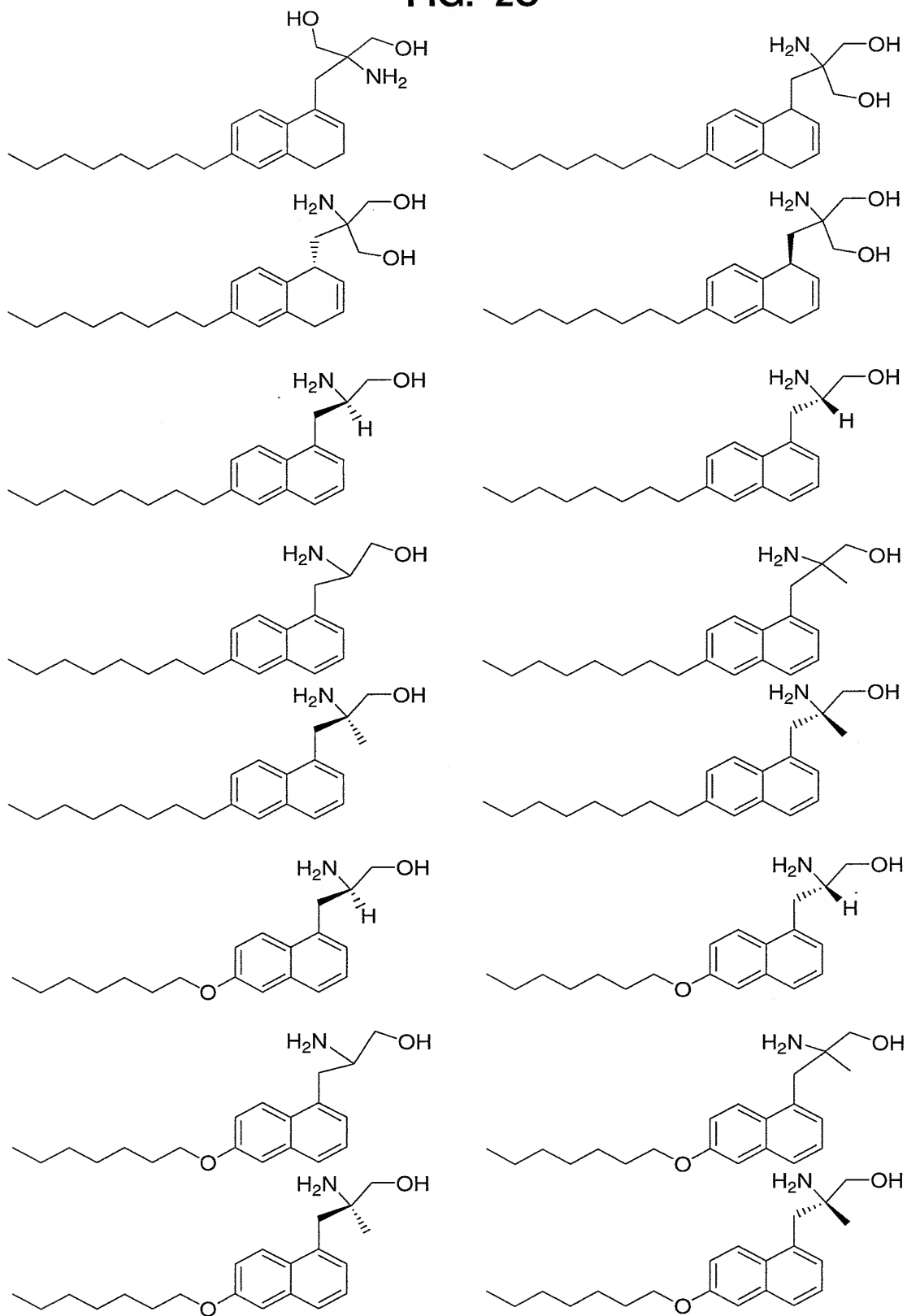
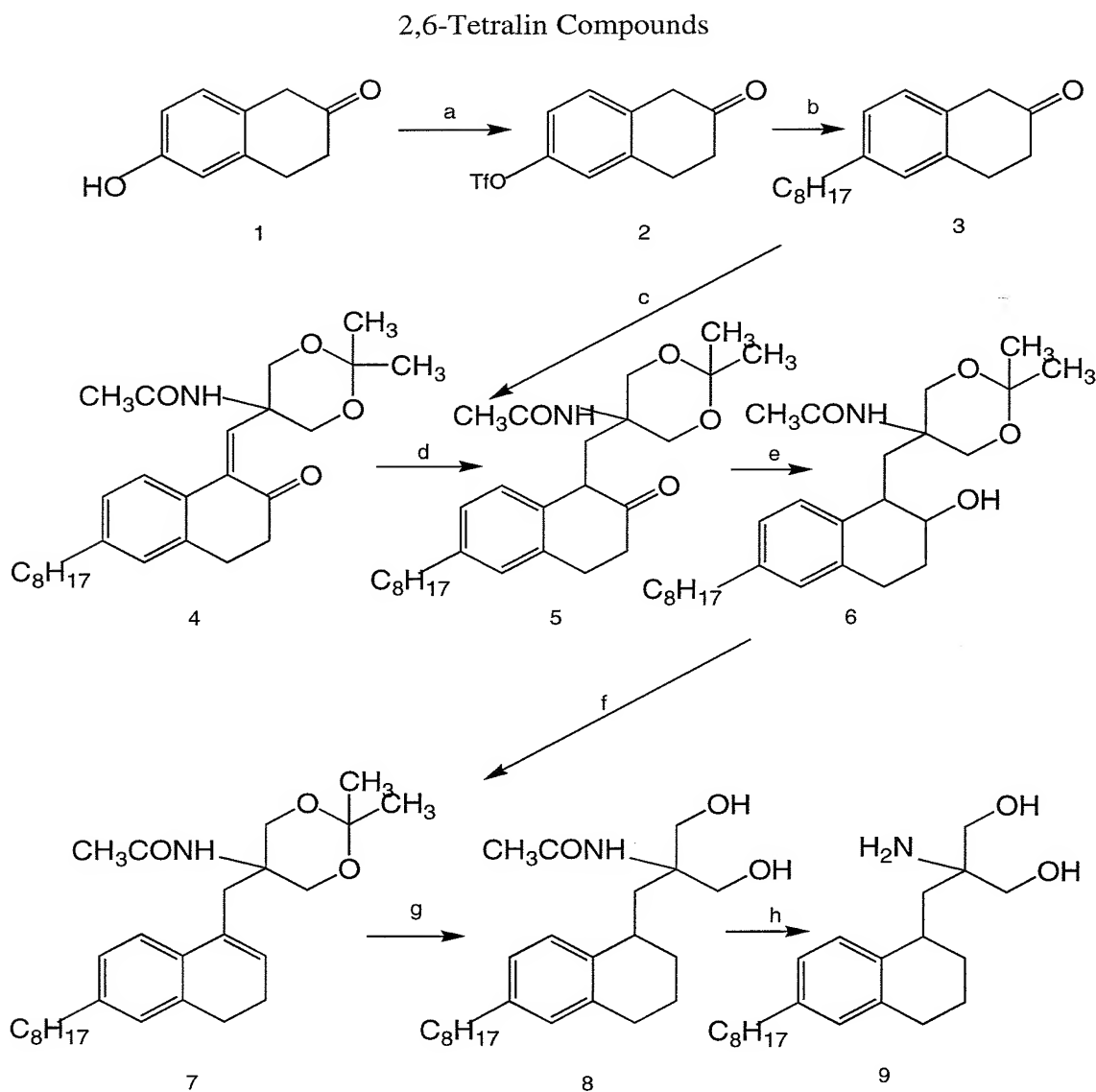


Fig. 3

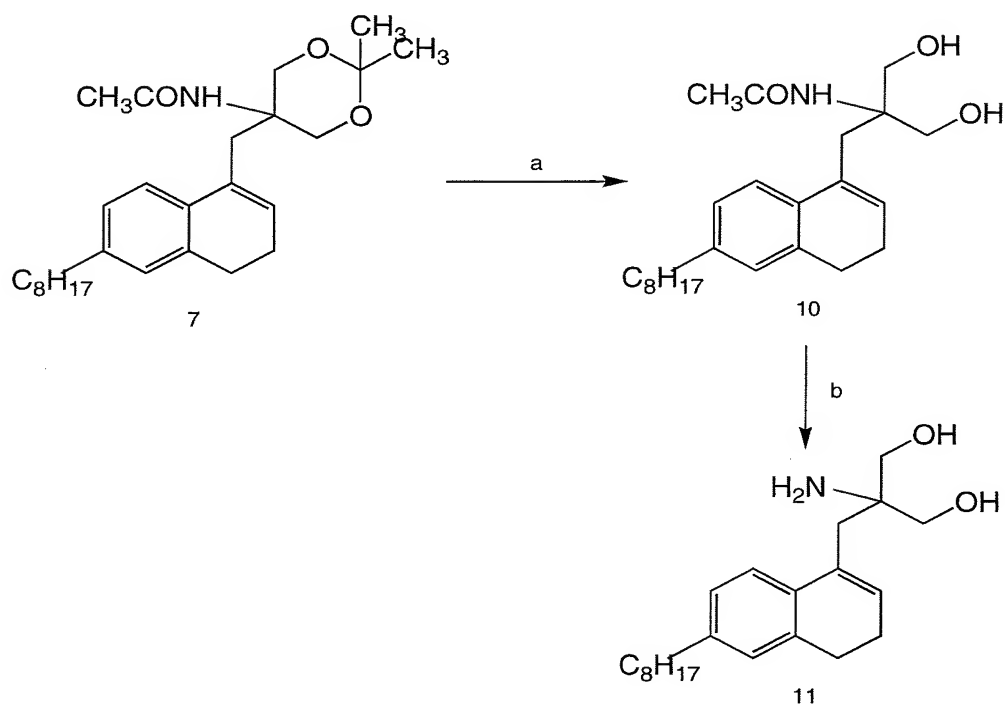
Scheme 1



Reagents and conditions: a) TiF_2O , 2,6-lutidine, CH_2Cl_2 , 0°C , 2h, 90%; b) 1-octene, 9-BBN, K_3PO_4 , KBr, H_2O , $\text{Pd}(\text{PPh}_3)_4$, 65°C , 2h, 72%; c) (i) KH, THF, -20 – -40°C ; (ii) 2,2-dimethyl-5-formyl-1,3-dioxan-5-yl carbamic acid tert-butyl ester; (iii) Ac_2O , TsOH; 20%; d) Pd/C , H_2 , EtOH, overnight, 0°C 45%; e) NaBH_4 , EtOH, rt, 3 h, 55%; f) TsOH, toluene, 70°C , 80%; g) (i) Pd/C , H_2 , EtOH; (ii) aqueous HCl, 3 hr, 70°C , 80%; h) LiOH, H_2O , MeOH, THF, 50°C , 5h, 75%;

Fig. 4**Scheme 2**

Unsaturated/Vinyl 2,5-Tetralin Compounds

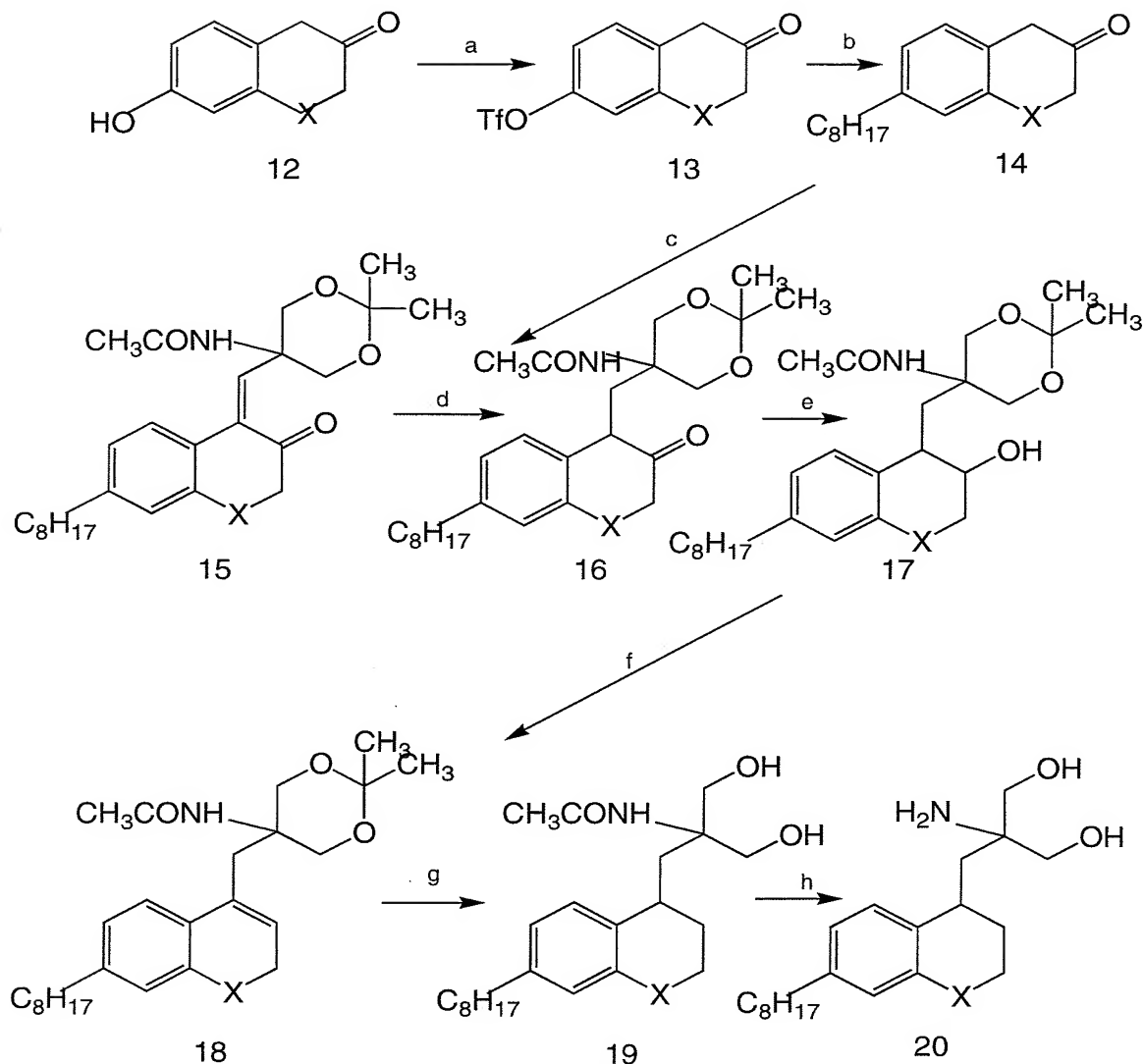


Reagents and conditions: a) EtOH, aqueous HCl, 6 hr, 70°C, 80%; b) LiOH, H₂O, MeOH, THF, 50°C, 5h, 75%;

Fig. 5

Scheme 3

2,5-Tetralin Hetero-compounds



X = O, S, NH, NR (R = C₁ to C₆ alkyl), NC(O)R

Reagents and conditions: a) Tf₂O, 2,6-lutidine, CH₂Cl₂, 0°C, 2h, 90%; b) 1-octene, 9-BBN, K₃PO₄, KBr, H₂O, Pd(PPh₃)₄, 65°C, 2h, 72%; c) (i) KH, THF, -20--40°C; (ii) 2,2-dimethyl-5-formyl-1,3-dioxan-5-yl)carbamic acid tert-butyl ester; (iii) Ac₂O, TsOH; 20%; d) Pd/C, H₂, EtOH, overnight, 0°C 45%; e) NaBH₄, EtOH, rt, 3 h, 55%; f) TsOH, toluene, 70°C, 80%; g) (i) Pd/C, H₂, EtOH; (ii) aqueous HCl, 3 hr, 70°C, 80%; h) LiOH, H₂O, MeOH, THF, 50°C, 5h, 75%;

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/085392

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D271/06 C07D333/16 C07D413/04 C07C215/38 A61K31/137
A61K31/381 A61K31/4245 A61P19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KOTERA, K. ET AL: "Stereochemistry of aziridine formation by reduction of oximes with lithium aluminum hydride on aralkyl alkyl ketoximes and their tosylates" XP002476746 retrieved from STN Database accession no. 1968:467158 abstract & TETRAHEDRON , 24(16), 5677-90 CODEN: TETRAB; ISSN: 0040-4020, 1968,</p> <p style="text-align: center;">----- -/--</p>	1-3, 17, 18

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

18 April 2008

Date of mailing of the international search report

28/04/2008

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Eberhard, Michael

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/085392

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/096757 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; ALBERT RAINER [CH]; EHRHA) 11 November 2004 (2004-11-11) examples 11-14 table 2 abstract -----	1-32
X	JP 2004 307442 A (KYORIN SEIYAKU KK) 4 November 2004 (2004-11-04) * Table 7, entries 11-14 *	1-32
P,X	WO 2007/092638 A (UNIV VIRGINIA [US]; LYNCH KEVIN R; MACDONALD TIMOTHY L [US]) 16 August 2007 (2007-08-16) the whole document -----	1-32

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/085392

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 20-28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2007/085392

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2004096757	A	11-11-2004	AU 2004234067 A1	11-11-2004
			BR PI0409977 A	09-05-2006
			CA 2523677 A1	11-11-2004
			EP 1622866 A1	08-02-2006
			JP 2006524662 T	02-11-2006
			MX PA05011597 A	15-12-2005
			US 2006211656 A1	21-09-2006
JP 2004307442	A	04-11-2004	NONE	
WO 2007092638	A	16-08-2007	NONE	